



US009365521B2

(12) **United States Patent**
Blackburn et al.

(10) **Patent No.:** **US 9,365,521 B2**
(45) **Date of Patent:** **Jun. 14, 2016**

(54) **NON-HYGROSCOPIC SALTS OF 5-HT_{2C} AGONISTS**

(75) Inventors: **Anthony C. Blackburn**, San Diego, CA (US); **Yun Shan**, San Diego, CA (US); **Anna Shifrina**, San Diego, CA (US); **Scott Stirn**, San Diego, CA (US)

(73) Assignee: **Arena Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 567 days.

(21) Appl. No.: **13/820,095**

(22) PCT Filed: **Aug. 31, 2011**

(86) PCT No.: **PCT/US2011/049960**

§ 371 (c)(1),

(2), (4) Date: **Aug. 8, 2013**

(87) PCT Pub. No.: **WO2012/030957**

PCT Pub. Date: **Mar. 8, 2012**

(65) **Prior Publication Data**

US 2013/0317005 A1 Nov. 28, 2013

Related U.S. Application Data

(60) Provisional application No. 61/402,611, filed on Sep. 1, 2010.

(51) **Int. Cl.**

C07D 223/16 (2006.01)

A61K 31/55 (2006.01)

A61K 45/06 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 223/16** (2013.01); **A61K 31/55** (2013.01); **A61K 45/06** (2013.01)

(58) **Field of Classification Search**

CPC C07D 223/16
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,900,415 A 8/1959 Biel
3,652,543 A 3/1972 Hoegerle
3,716,639 A 2/1973 Hoegerle et al.
3,795,683 A 3/1974 Brossi et al.
4,108,989 A 8/1978 Holden
4,111,957 A 9/1978 Holden et al.
4,210,729 A 7/1980 Hermans et al.
4,210,749 A 7/1980 Shetty
4,233,217 A 11/1980 Shetty
4,477,378 A 10/1984 Gold et al.
4,541,954 A 9/1985 Borowski et al.
4,584,293 A 4/1986 Reiffen et al.
4,737,495 A 4/1988 Bomhard et al.
4,762,845 A 8/1988 Chu et al.
4,957,914 A 9/1990 Clark et al.
4,988,690 A 1/1991 Effland et al.
5,015,639 A 5/1991 Berger et al.

5,178,786 A	1/1993	Jahnke et al.	
5,247,080 A	9/1993	Berger et al.	
5,275,915 A	1/1994	Kojima et al.	
5,387,685 A	2/1995	Powell et al.	
5,397,793 A	3/1995	Shaber et al.	
5,412,119 A	5/1995	Brussee et al.	
5,422,355 A	6/1995	White et al.	
5,691,362 A	11/1997	McCormick et al.	
5,750,520 A	5/1998	Danilewicz et al.	
5,795,895 A	8/1998	Anchors	
5,856,503 A	1/1999	Aebi et al.	
5,861,393 A	1/1999	Danilewicz et al.	
5,908,830 A	6/1999	Smith et al.	
5,925,651 A	7/1999	Hutchinson	
5,939,415 A	8/1999	Laufer et al.	
5,942,535 A	8/1999	Laufer et al.	
5,958,943 A	9/1999	Laufer et al.	
6,087,346 A	7/2000	Glennon et al.	
6,218,385 B1	4/2001	Adam et al.	
6,900,313 B2	5/2005	Wasserscheid et al.	
6,953,787 B2 *	10/2005	Smith	C07D 223/16 514/212.02
6,972,295 B2	12/2005	Hagmann et al.	
7,053,192 B2 *	5/2006	Li	A61K 9/1688 536/7.4
7,105,523 B2	9/2006	Stasch et al.	
7,157,466 B2	1/2007	McClure et al.	
7,173,037 B2	2/2007	Alonso-Alija et al.	
7,211,591 B2	5/2007	Tajima et al.	
7,229,991 B2	6/2007	Merla et al.	
7,230,024 B2	6/2007	Carpino et al.	
7,232,823 B2	6/2007	Carpino et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

AU	515 236 B2	3/1981
CA	1090797	12/1980

(Continued)

OTHER PUBLICATIONS

Berge et al. J. Pharm. Sci. 1997, 66, pp. 1-19.*
Stahl et al. Handbook of Pharmaceutical Salts, 2002, pp. 286 and 287.*
Background Information for the October ACPS Meeting, FDA, 2002.*
B. Rodriguez-Spong et al. Advanced Drug Delivery Reviews, 2004, 56, pp. 241-274.*
Hilfiker, R. Polymorphism in the Pharmaceutical Industry, Wiley, 2006, 213-216.*
U.S. Appl. No. 60/372,058, filed Apr. 12, 2002, Smith et al.
U.S. Appl. No. 60/405,495, filed Aug. 23, 2002, Smith et al.
U.S. Appl. No. 60/434,607, filed Dec. 18, 2002, Smith et al.
U.S. Appl. No. 60/479,280, filed Jun. 17, 2003, Smith et al.
U.S. Appl. No. 60/512,967, filed Oct. 21, 2003, Burbaum et al.
U.S. Appl. No. 60/638,221, filed Dec. 21, 2004, Agarwal et al.

(Continued)

Primary Examiner — Matthew Coughlin

(74) Attorney, Agent, or Firm — Fish & Richardson P.C.;
Lyle W. Spruce

(57) **ABSTRACT**

Salts of the 5-HT_{2C}-receptor agonist (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and dosage forms comprising them that are useful for, inter alia, weight management.

26 Claims, 21 Drawing Sheets

(56)

References Cited

U.S. PATENT DOCUMENTS

7,514,422	B2 *	4/2009	Smith	C07D 223/16
					514/212.02
7,704,993	B2	4/2010	Smith et al.		
7,977,329	B2 *	7/2011	Smith	C07D 223/16
					514/212.02
8,153,621	B2 *	4/2012	Behan	A61K 31/135
					514/212.02
8,168,624	B2	5/2012	Agarwal et al.		
8,168,782	B2	5/2012	Weigl et al.		
8,207,158	B2 *	6/2012	Smith	C07D 223/16
					514/212.02
8,273,734	B1 *	9/2012	Smith	C07D 223/16
					514/212.02
8,299,241	B2	10/2012	Gharbaoui et al.		
8,546,379	B2 *	10/2013	Smith	C07D 223/16
					514/212.02
8,575,149	B2 *	11/2013	Smith	C07D 223/16
					514/212.02
8,952,197	B2 *	2/2015	DeMattei	C07C 17/16
					564/376
8,993,750	B2 *	3/2015	Smith	C07D 223/16
					540/594
8,999,970	B2 *	4/2015	Anderson	A61K 31/55
					436/98
9,102,627	B2 *	8/2015	Wolgast	C07C 209/50
2003/0105106	A1	6/2003	Chiang et al.		
2003/0225057	A1	12/2003	Smith et al.		
2004/0101575	A1	5/2004	Hinz		
2005/0020573	A1	1/2005	Smith et al.		
2005/0135999	A1 *	6/2005	Elomari	C01B 39/48
					423/706
2007/0032435	A1 *	2/2007	Alani	A61K 31/425
					536/23.74
2007/0060568	A1	3/2007	Smith et al.		
2007/0134803	A1 *	6/2007	Blatter	B01J 19/0046
					436/96
2007/0142357	A1 *	6/2007	Smith	A61K 31/55
					514/217.01
2007/0249544	A1 *	10/2007	Himmelsbach	C07H 15/00
					514/27
2007/0275949	A1	11/2007	Smith et al.		
2008/0004448	A1 *	1/2008	Wayne	C07D 487/04
					546/276.7
2008/0009478	A1	1/2008	Smith et al.		
2008/0045502	A1	2/2008	Wolgast et al.		
2008/0089835	A1 *	4/2008	Burton	C01B 39/48
					423/706
2008/0103186	A1 *	5/2008	Glover	A61K 31/4184
					514/395
2008/0139569	A1 *	6/2008	Rocco	C07D 487/04
					514/248
2008/0319024	A1 *	12/2008	Greil	C07D 417/12
					514/342
2009/0069281	A1 *	3/2009	Austad	A61K 9/146
					514/183
2009/0124652	A1 *	5/2009	Ach	C07D 471/14
					514/293
2009/0137794	A1 *	5/2009	Mendez	C07J 43/003
					540/78
2009/0143576	A1	6/2009	Weigl et al.		
2009/0176983	A1 *	7/2009	Dova	C07F 9/65616
					544/242
2009/0197868	A1 *	8/2009	Behan	A61K 31/135
					514/215
2009/0203705	A1 *	8/2009	Biagetti	C07D 413/12
					514/252.02
2009/0239946	A1 *	9/2009	McKeown	A61K 31/295
					514/494
2010/0004223	A1 *	1/2010	Agarwal	C07D 223/16
					514/217.01
2010/0021539	A1 *	1/2010	Kowalski	A61K 9/2018
					424/464
2010/0173894	A1	7/2010	Smith et al.		
2010/0305316	A1	12/2010	Gharbaoui et al.		
2011/0015438	A1	1/2011	Carlos et al.		

2012/0135982	A1	5/2012	Smith et al.
2012/0142967	A1	6/2012	De Mattei et al.
2012/0252786	A1	10/2012	Behan et al.
2012/0252787	A1	10/2012	Anderson et al.
2012/0252788	A1	10/2012	Smith et al.
2012/0264743	A1	10/2012	Agarwal et al.

FOREIGN PATENT DOCUMENTS

CA	2197789	2/1996
CA	2325741	10/1999
CH	500194	1/1971
CN	102126988	7/2011
DE	1944121	3/1970
DE	1914456	6/1971
DE	3315106	A1 11/1983
DE	3418270	A1 11/1985
EP	0 002 765	A1 7/1979
EP	0 027 695	B1 10/1980
EP	0 007 070	A1 1/1983
EP	0 161 350	A1 11/1985
EP	0 174 118	A3 3/1986
EP	0 080 779	B1 7/1986
EP	0 204 349	A2 12/1986
EP	0 096 838	A1 4/1987
EP	0 245 997	A2 11/1987
EP	0 285 287	A2 10/1988
EP	0 285 287	A3 10/1988
EP	0 331 130	A1 9/1989
EP	0 331 130	B1 9/1993
EP	0 285 919	B1 10/1994
EP	0 987 235	A1 3/2000
EP	1 074 549	A2 2/2001
EP	0 987 235	B1 3/2003
EP	1 074 549	B1 11/2003
EP	1 411 881	A2 4/2004
EP	1 411 881	B1 5/2005
EP	1 838 677	B1 9/2009
FR	2 518 544	A1 6/1983
GB	1196229	6/1970
GB	1221324	2/1971
GB	1225053	3/1971
GB	1247306	9/1971
GB	1268243	3/1972
GB	1542317	3/1979
GB	1599705	10/1981
GB	2133401	7/1984
JP	62-267250	11/1987
JP	2-502723	8/1990
JP	5-339263	12/1993
JP	6-62574	8/1994
JP	6-298746	10/1994
JP	8-134048	5/1996
JP	9-30960	2/1997
JP	9-87258	3/1997
JP	2000-44533	2/2000
JP	2001-76413	3/2001
JP	2001-89472	4/2001
NL	7807819	7/1978
SU	1238732	A3 6/1986
WO	WO 88/07526	A1 10/1988
WO	WO 88/07858	A1 10/1988
WO	WO 91/19698	A1 12/1991
WO	WO 93/00094	A2 1/1993
WO	WO 93/03015	A1 2/1993
WO	WO 93/16997	A1 9/1993
WO	WO 95/13274	A1 5/1995
WO	WO 96/04271	A1 2/1996
WO	WO 96/05194	A1 2/1996
WO	WO 96/33993	A1 10/1996
WO	WO 97/24364	A1 7/1997
WO	WO 98/06701	A1 2/1998
WO	WO 98/40385	A1 9/1998
WO	WO 99/24411	A1 5/1999
WO	WO 02/40471	A2 5/2002
WO	WO 02/48124	A2 6/2002
WO	WO 02/07476	A1 9/2002
WO	WO 03/000663	A1 1/2003
WO	WO 03/027068	A2 4/2003

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO 03/057161	A2	7/2003
WO	WO 03/062205	A1	7/2003
WO	WO 03/062392	A2	7/2003
WO	WO 03/086306	A2	10/2003
WO	WO 03/086306	A3	2/2004
WO	WO 2004/037788	A1	5/2004
WO	WO 2005/003096	A1	1/2005
WO	WO 2005/016902	A1	2/2005
WO	WO 2005/019179	A2	3/2005
WO	WO 2005/019179	A3	3/2005
WO	WO 2005/019180	A1	3/2005
WO	WO 2005/042490	A1	5/2005
WO	WO 2005/042491	A1	5/2005
WO	WO 2005/082859	A1	9/2005
WO	WO 2006/006933	A2	1/2006
WO	WO 2006/013209	A2	2/2006
WO	WO 2006/043710	A1	4/2006
WO	WO 2006/069363	A2	6/2006
WO	WO 2006/071740	A2	7/2006
WO	WO 2006/069363	A3	5/2007
WO	WO 2007/120517	A2	10/2007
WO	WO 2007/120517	A3	6/2008
WO	WO 2008/070111	A2	6/2008
WO	WO 2008/070111	A3	8/2008
WO	WO 2008/153632	A2	12/2008
WO	WO 2008/156707	A1	12/2008
WO	WO 2009/080691	A2	7/2009
WO	WO 2009/097416	A1	8/2009
WO	WO 2009/111004	A1	9/2009
WO	WO 2010/148207	A2	12/2010
WO	WO 2012/030927	A2	3/2012
WO	WO 2012/030938	A1	3/2012
WO	WO 2012/030951	A1	3/2012
WO	WO 2012/030953	A1	3/2012

OTHER PUBLICATIONS

U.S. Appl. No. 60/789,191, filed Apr. 3, 2006, Lu et al.
 U.S. Appl. No. 60/873,036, filed Dec. 5, 2006, Gharbaoui et al.
 U.S. Appl. No. 61/068,102, filed Mar. 4, 2008, Carlos et al.
 U.S. Appl. No. 61/268,930, filed Jun. 18, 2009, Demattei et al.
 "Arena Pharmaceuticals Announces Results of its Phase 1b Safety Study for its Novel Anti-Obesity Compound," Press Release, Nov. 30, 2004, 2 pages.
 "Arena Pharmaceuticals Initiates Clinical Trial of Novel Anti-Obesity Drug," Press Release, Feb. 24, 2004, 1 page.
 "Arena Pharmaceuticals Initiates Phase 1b Clinical Trial of Novel Anti-Obesity Drug," Press Release, Jul. 26, 2004, 1 page.
 "Arena Pharmaceuticals Initiates Phase 2 Efficacy Study for its Novel Anti-Obesity Compound," Press Release, Dec. 22, 2004, 2 pages.
 "Arena Pharmaceuticals Reports Successful Phase 1a Safety and Clinical Pharmacology Trial Results of Novel Anti-Obesity Compound," Press Release, Jul. 14, 2004, 2 pages.
 "Silver Lining to the Cloud Over Anorexigen-Related Cardiac Valvulopathy?" Editorial, *Annals of Internal Medicine*, 134(4): 335-337 (2001).
 Bagnol et al., "Obesity and Hypothalamic Signaling: Role of GPCRs," Presentation, Arena Pharmaceuticals, Inc., Jul. 30, 2010, 30 pages.
 Baidur et al., "(±)-3-Allyl-7-halo-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines as Selective High Affinity D1 Dopamine Receptor Antagonists: Synthesis and Structure-Activity Relationship," *J. Med. Chem.*, 35:67-72 (1992).
 Barbieri, "Estérification Nitrique et Nitration d'Amino-alcools," *Bulletin de la Société Chimique de France*, 5(11):470-480 (1944).
 Barnes, "Pharmacological Strategies for Relapse Prevention in Schizophrenia," *Psychiatry* 3(10): 37-40 (2004).
 Berge et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences* 66(1):1-19 (1977).
 Bickerdike, "5-HT_{2C} Receptor Agonists as Potential Drugs for the Treatment of Obesity," *Current Topics in Medicinal Chemistry*, 3:885-897 (2003).

Biel, "Bronchodilators, N-substituted Derivatives of 1-(3',4'-Dihydroxyphenyl)-2-aminoethanol (Arterenol)," *J. Am. Chem. Soc.* 76:3149-3153 (1954).
 Binetti et al. "Behavior Disorders in Alzheimer Disease: A Transcultural Perspective," *Arch Neurol.*, 55:539-544 (1998).
 Bosch et al., "Studies on the Synthesis of Pentacyclic Strychnos Indole Alkaloids. Photocyclization of N-Chloroacetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino [4,3-b] Indole Derivatives," *Tetrahedron*, 41(12):2557-66 (1985).
 Bos et al., "Novel Agonists of 5HT_{2C} receptors. Synthesis & biological evaluation of Substituted 2-(Indol-1-yl)-1-methylethylamines and 2-(Indeno[1,2-b]pyrrol-1-yl)-1-methylethylamines," *Improved Therapeutics for Obsessive Compulsive Disorder*, *J. Med. Chem.* 40(17):2762-2769 (1997).
 Bremner "Seven Membered Rings," *Institute for Biomolecular Science, Dept. of Chemistry, University of Wollongong*; "Progress in Heterocyclic Chemistry 13," Pergamon Press, Ch. 7:340-77 (2001).
 Byrn et al., "Pharmaceutical solids: A strategic approach to regulatory consideration," *Pharmaceutical Research* 12(7):945-954 (1995).
 Cairn, "Crystalline polymorphism of organic compounds," *Topics in Current Chemistry* 198(2): 163-208 (1998).
 Callahan et al., "Fluoxetine Increases the Anorectic and Long-Term Dopamine-Depleting Effects of Phentermine," *Synapse*, 38(4):471-6 (2000).
 Carey, F and Sundberg, R., "Advanced Organic Chemistry, Part B: Reactions and Synthesis, second edition" 1983, Plenum Press, New York, pp. 96-98.
 CAS Registry No. 006640-24-01 (2007).
 CAS Registry No. 27487-50-9 (1984).
 CAS Registry No. 27487-51-0 (1984).
 CAS Registry No. 46906-45-0 (1984).
 CAS Registry No. 149454-12-6 (1993).
 CAS Registry No. 400878-20-8 (2002).
 CAS Registry No. 620948-34-7 and 620948-93-8 (2007).
 Casy, et al., "Some Arylalkylamino Analogs of Acyclic Analgetics," *J. Med. Chem.*, 11(3):599-601 (1968).
 Chahal et al., IDdb Meeting Report May 17-18, 2000.
 Chang et al., "Dopamine Receptor Binding Properties of Some 2,3,4,5-tetrahydro-1H-3-benzazepine-7-ols with Non-Aromatic Substituents in the 5-Position," *Bioorganic & Medicinal Chemistry Letters*, 2(5):399-402 (1992).
 Chemical abstract (online) Accession No. 1980:407990, 1980.
 Cheng, "Fen/Phen and Valvular Heart Disease: The Final Link Has Now Been Established," *Circulation* 2000;102:e180.
 Chumpradit et al., "(±)-7-Chloro-8-hydroxy-1-(4'-[125I]iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine: A Potential CNS D-1 Dopamine Receptor Imaging Agent," *J. Med. Chem.*, 32:1431-35 (1989).
 Clark et al., "1,9-Alkano-bridged 2,3,4,5-tetrahydro-1H-3-benzazepines with Affinity for the α₂-Adrenoceptor and the 5-HT_{1A} Receptor," *J. Med. Chem.*, 33:633-41 (1990).
 Clinical Trial NCT00768612. "Study Evaluating Safety and Tolerability of Vabicaserin in Patients With Sudden Worsening of Schizophrenia Study," (2008).
 Connolly et al., "Selections from Current Literature: Pharmacological Treatment of Obesity," *Family Practice*, 15(1):88-93 (1998).
 Deady et al., "Synthesis of Some Tetrahydro-2- and 3-benzazepines, and of Hexahydro-3-benzazocine," *JCS Perkin I*, 782-3 (1973).
 Demarinis et al., "Development of an Affinity Ligand for Purification of α₂-Adrenoceptors from Human Platelet Membranes," *J. Med. Chem.*, 27:918-921 (1984).
 Dhonchadha et al., "Anxiolytic-Like Effects of 5-HT₂ Ligands on Three Mouse Models of Anxiety," *Behav. Brain Res.* 140:203-214 (2003).
 Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision, Washington, DC, American Psychiatric Association, 2000.
 Di Chiara et al., "Nucleus Accumbens Shell and Core Dopamine: Differential Role in Behavior and Addiction," *Behavioural Brain Research*, 137: 75-114 (2002).
 Di Chiara et al., "Reward System and Addiction: What Dopamine Does and Doesn't Do," *Current Opinion in Pharmacology* 7:69-76 (2007).

(56)

References Cited

OTHER PUBLICATIONS

- Di Giovanni et al., "Serotonin/Dopamine Interaction—Focus on 5-HT_{2C} Receptor, A New Target of Psychotropic Drugs," *Indian Journal of Experimental Biology*, 40:1344-1352 (2002).
- Di Matteo et al., "Role of 5-HT_{2C} Receptors in the Control of Central Dopamine Function," *Trends in Pharmacological Sciences*, 22(5):229-232 (2001).
- Dixit et al., "Agents Acting on Central Nervous System: Part XXIII—2-Substituted 1, 2, 3, 4, 6, 7, 12, 12a-Octahydropyrazino[2,1-b][3] benzazepines & 3-Substituted 1, 2, 3, 4, 4a, 5, 6, 11-Octahydropyrazino[1,2-b][2] benzazepines," *CDRI Communication No. 1969*, 893-97 (1974).
- Draper et al., "Novel Stereoselective Syntheses of the Fused Benzazepine Dopamine D₁ Antagonist (6aS, 13bR)-11-chloro-6, 6a,7,8,9, 13b-hexahydro-7-methyl-5H-benzo[d]naphth[2, 1-b]azepin-12-ol (Sch 39166): 1. Aziridinium Salt Based Syntheses," *Organic Process Research & Development*, 2(3):175-85 (1998).
- Flannery-Schroeder, "Reducing Anxiety to Prevent Depression," *Am. J. Prev. Med.* 31 (6S1):S136-S142 (2006).
- Frankel et al., "Brain Serotonin Transporter Distribution in Subjects With Impulsive Aggressivity: A Positron Emission Study With [11C]McN 5652," *Am. J. Psychiatry*, 162:915-923 (2005).
- Fuchs et al., "Total Synthesis of (+/-)-Lennoxamine and (+/-)-Aphanorphine by Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins," *Organic Letters*, 3(24):3923-3925 (2001).
- Gallant et al., "U-22,394A: A Controlled Evaluation in Chronic Schizophrenic Patients," *Current Therapy Research*, 9(11):579-81 (1967).
- Gardent et al., "Sur Quelques Propriétés De L' amino-2-Bromo-4 1H Benzazepine-3 Et De Ses Derivés," *Bulletin de la Société Chimique de France*, 2:600-5 (1968).
- Garrido., *Form and Structure of Crystals*, Chapter V, p. 204.
- Garrison, "Defining Obesity: An Adventure in Cardiovascular Disease Epidemiology," *J. Nutritional Biochem.* 9(9):493-500 (1998).
- Gerace et al., "Predictors of Weight Increases over 7 Years in Fire Fighters and Paramedics," *Preventive Medicine* 25:593-600 (1996).
- Gerritz et al., "Two General Routes to 1,4-Disubstituted-2,3,4,5-tetrahydro-1H-3-benzazepines," *Organic Letters*, 2(25):4099-102 (2000).
- Gobert et al., "Serotonin_{2c} Receptors Tonically Suppress the Activity of Mesocortical Dopaminergic and Adrenergic, But Not Serotonergic, Pathways: A Combined Dialysis and Electrophysiological Analysis in the Rat," *Synapse* 36: 205-221 (2000).
- Gombar et al., "Pharmacokinetics of a Series of 6-Chloro-2, 3, 4, 5-Tetrahydro-3-Substituted-1H-3-Benzazepines in Rats," *Drug Metab. Disposition*, 16:367-372 (1988).
- Greene, "Protective Groups in Organic Synthesis," 3rd Ed., Wiley and Sons (1999).
- Greene et al., *Protective Groups in Organic Syntheses*, 2nd Ed., Wiley and Sons, NY (1991).
- Griesser "Polymorphism in the Pharmaceutical Industry," ed. Rolf Hilfer, Wiley-VCH Verlag GmbH & Co.: pp. 211-233 (2006).
- Guillory, "Polymorphism in Pharmaceutical Solids," ed. Harry G. Brittain, Marcel Dekker, Inc., vol. 95: pp. 202-209 (1999).
- Halford et al., "Serotonergic Drugs: Effects on Appetite Expression and Use for the Treatment of Obesity," *Drugs* 67(1):27-55 (2007).
- Halford et al., "o-Phenylenediacetamide and Other Compounds Related to 3,1H-benzazepine," *J. Org. Chem.*, 17:1646-52 (1952).
- Halford, "Obesity Drugs in Clinical Development," *Current Opinion in Investigational Drugs* 7(4):312-318 (2006).
- Hasan et al., "Syntheses of N-Chloroacetyl-β-phenylethylamine Derivatives," *Indian J. Chem.*, 9:1022-4 (1971).
- Hashima et al., "Syntheses and Biological Activities of the Marine Bryozoan Alkaloids Convolutamines A, C and F and Lutamides A and C," *Bioorg & Med. Chem.*, 8:1757 (2000).
- Hassine-Coniac, et al., "Préparation Et Propriétés D' aldéhydes Dans La Série De La Benzazépine-3," *Bulletin de La Société Chimique de France*, 11:3985-92 (1971) French Lang Only.
- Haynes et al., "Occurrence of Pharmaceutically Acceptable Anions and Cations in the Cambridge Structural Database," *J. Pharm. Sci.* 94(10):2111-2120 (2005).
- Hazebrucq, "Accès A Des I-H, Tétrahydro-2, 3, 4,5 Benzazépines-3 One-I, et a Des Hexahydro Imidazo Isoquinoléines," *Ann. Chim.*, t.1:221-54 (1966) French Lang Only.
- Heisler et al., "Activation of Central Melanocortin Pathways by Fenfluramine," *Science*, 297:609-611 (2002).
- Helfferich et al., "Über Derivate Einger Chinolincarbonsäuren," *J. Fur Praktische Chemie*, 33:39-48 (1966).
- Hester et al., "Azepinoindoles. I. Hexahydroazepino[4,5-b]indoles," *J. Med. Chem.*, 11(1): 101-106 (1968).
- Heys et al., "A New Entry into C7-Oxygenated Tetrahydro-1H-3-benzazepines: Efficient Labeling with Carbon-14 in the Benzo Ring," *J. Org. Chem.*, 54(19):4702-6 (1989).
- Higgins et al., "Serotonin and Drug Reward: Focus on 5-HT_{2C} Receptors," *European Journal of Pharmacology*, 480: 151-162 (2003).
- Hitzig, "Combined Serotonin and Dopamine Indirect Agonists Correct Alcohol Craving and Alcohol-Associated Neuroses," *Journal of Substance Abuse Treatment*, 11(5):489-90 (1994).
- Ichii, "Friedel-Crafts Alkylation. II. The AlCl₃ CH₂NO₂-Catalyzed Phenethylation of Benzene and Toluene With 2-Arylethyl Chlorides in a Nitromethane Solution," *Bulletin of the Chemical Society of Japan*, 45(9):2810-2813 (1972).
- Im et al., "Positive Allosteric Modulator of the Human 5-HT_{2C} Receptor," *Molecular Pharmacology*, 64: 78-84 (2003).
- Isaac, "The 5-HT_{2C} Receptor as a Potential Therapeutic Target for the Design of Antiobesity and Antiepileptic Drugs," *Drugs of the Future* 26(4), 383-393 (2001).
- Jandacek, "APD-356 (Arena)," *Current Opinion in Investigational Drugs* 6(10):1051-1056 (2005).
- Jenck, et al., "Antiaversive Effects of 5HT_{2C} Receptor Agonists and Fluoxetine in a Model of Panic-Like Anxiety in Rats," *European Neuropsychopharmacology* 8: 161 (1998).
- Jensen et al., "Potential Role of New Therapies in Modifying Cardiovascular Risk in Overweight Patients with Metabolic Risk Factors," *Obesity* 14 (Suppl. 3):143S-149S (2006).
- Kaiser et al., "6-(Phenylthio)-substituted 2,3,4,5-tetrahydro-1H-3-benzazepines, A Novel Class of Dopamine Receptor Antagonists and Neuroleptics," *J. Med. Chem.*, 23(9):975-6 (1980).
- Karasu et al., *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* (2000).
- Klein, "Outcome Success in Obesity," *Obesity Res.*, 9(suppl. 4):354S-358S (2001).
- Klohr et al., "An Intramolecular Photocyclization to Form the Azepino[3,4,5-cd]Indole System," *Synthetic Communications* 18(7):671-4 (1988).
- Koplan et al., "Preventing Childhood Obesity: Health in the Balance, Executive Summary," *The National Academies Press*, Washington, D.C., 436 pages (excerpt includes pp. 1-19, v-xix) (2005).
- Krull et al., "Synthesis and Structure/NMDA Receptor Affinity Relationships of 1-Substituted Tetrahydro-3-Benzazepines," *Bioorganic & Medicinal Chem.* 12(6):1439-1451 (2004).
- Kuenburg et al., "Development of a Pilot Scale Process for the Anti-Alzheimer Drug (-)-Galanthamine Using Large-Scale Phenolic Oxidative Coupling and Crystallisation-Induced Chiral Conversion," *Organic Process Research & Development*, 3(6):425-31 (1999).
- Lacivita et al., "Selective Agents for Serotonin_{2C} (5-HT_{2C}) Receptor," *Current Topics in Medicinal Chemistry*, 6: 1927-1970 (2006).
- Ladd et al., "Synthesis of a Dopaminergic Binding of 2-Aryldopamine Analogues: Phenethylamines, 3-Benzazepines, and 9-(Aminomethyl) Fluorenes," *J. Med. Chem.*, 29(10):1904-12 (1986).
- Lam et al., *Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder*, Clinical & Academic Publishing, Vancouver, BC, Canada (1999).
- Lanteri et al., "Drugs of abuse specifically sensitive noradrenergic and serotonergic neurons via a non-dopaminergic mechanism," *Neuropsychopharmacology* 33(7):1724-1734 (2008).
- Lennon et al., "Azabenzocycloheptenones. Part XVIII. Amines and Amino-ketones of the Tetrahydro-3-benzazepin-1-one Series," *J.C. S. Perkin I*, 7:622-6 (1975).

(56)

References Cited

OTHER PUBLICATIONS

- Lin et al., "Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction," *J. Org. Chem.*, 52(25):5594-601 (1987).
- Loke et al., "Appetite Suppressants and Valvular Heart Disease—A Systematic Review," *BMC Clinical Pharmacology*, 2(6):1-10 (2002).
- MacDonald et al., "Design and Synthesis of trans-3-(2-(4-((3-(3-(5-methyl-1,2,4-oxadiazolyl))-phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SB-414796): A Potent and Selective Dopamine D3 Receptor Antagonist," *J. Med. Chem.*, 46(23):4952-64 (2003).
- March, "Advanced Organic Chemistry, Reactions, Mechanisms and Structure; Third edition," 1985, John Wiley & Sons (Wiley-Interscience Publication), New-York, pp. 382-384.
- Martin et al., "5HT2C Receptor Agonists Pharmacological Characteristics and Therapeutic Potential," *J. Pharmacol. Exp. Therap.*, 286(2):913-924 (1998).
- Millan et al., "5HT2C Receptors Mediate Penile Erections in Rats: Actions of Novel and Selective Agonists and Antagonists," *Eur. J. Pharmacol.*, 325:9-12 (1997).
- Millan et al., "Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo," *Neuropharmacology* 37(7):953-955 (1998).
- Moline et al., "Postpartum Depression: A Guide for Patients and Families," Expert Consensus Guidelines Series—Treatment of Depression in Woman, 112-113 (2001).
- Mondeshka et al., "Racemische und optisch active 2-Chlorethylcarbamoyl-Derivate des 7,8-Dimethoxy-1-phenyl-1H-3-benzazepins: Neue Strukturtypen von DA, NE und 5-HT Uptake Inhibitoren," *Arch. Pharm.*, 323:829-832 (1990).
- Morisette et al., "High-throughput crystallization: polymorphs, salts, co-crystals and solcates of pharmaceutical solids," *Advanced Drug Delivery Reviews* 56(3):275-300 (2004).
- Muller et al., "Intracellular 5-HT2C-Receptor Dephosphorylation: A New Target for Treating Drug Addiction," *Trends in Pharmacological Sciences*, 27(9):455-58 (2006).
- Nagase et al., "An Anhydrous Polymorphic Form of Trehalose," *Carbohydrate Research* 337(2):167-173 (2002).
- Nagle et al., "Efficient Synthesis of β -amino Bromides," *Tetrahedron Letters*, 41:3011-4 (2000).
- Nair et al., "Preparation of 2,3,4,5-Tetrahydro-3,1H-benzazepine-2-one," *Indian J. Chem.*, 5:169-70 (1967).
- National Institute on Drug Abuse, Proc. 41st Ann. Scientific Mtg. 356-401 (1979).
- Navarro-Vazquez et al., "A Study of Aryl Radical Cyclization in Enaminone Esters," *J. Org. Chem.*, 67:3213-20 (2002).
- Neumeyer et al., "Development of a High Affinity and Stereoselective Photoaffinity Label for the D-1 Dopamine Receptor: Synthesis and Resolution of 7-[125I]Iodo-8-hydroxy-3-methyl-1-(4'-azidophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine," *J. Med. Chem.*, 33(2):521-6 (1990).
- Niendam et al., "Neurocognitive Performance and Functional Disability in the Psychosis Prodrome," *Schizophrenia Research*, 84:100-111 (2006).
- Ohnmacht et al., "Naphtho[2,1-b][1,5]- and [1,2-f][1,4]oxazocines as Selective NK1 Antagonists," *Biorganic & Medicinal Chem.* 12(10):2653-2666 (2004).
- Okuno et al., "Photocyclization of N-chloroacetyl-2,5-dimethoxyphenethylamine. Synthesis of Pyrroloindoles," *Chem. Pharm. Bull.*, 23(11):2584-90 (1975).
- Orito et al., "Benzolactams-1: Alkylation of 1,2,4,5-Tetrahydro-3-Methyl-3H-3-Benzazepin-2-One With Sodium Hydride and Alkyl Halide," *Tetrahedron* 36:1017-1021 (1980).
- Orito et al., "Total Synthesis of Pseudo Type of Protopine Alkaloids," *Heterocycles*, 14(1):11-14 (1980).
- Orito, et al., "Synthetic Studies of Heterocyclic Compounds I. Alkylation and Acylation of 1,2,4,5-Tetrahydro-3-Methyl-3H-3-Benzazepin-2-one," *CASREACT*, 93:7990 (1979).
- Paulekuhn et al., "Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database," *J. Med. Chem.*, 50(26):6665-6672 (2007).
- Pauvert et al., "Silver Nitrate-Promoted Ring Enlargement of 1-tribromomethyl-1,2-dihydro- and 1-tribromomethyl-1,2, 3,4-tetrahydro-isoquinoline Derivatives: Application to the Synthesis of the Anti-anginal Zatebradine," *Tetrahedron Letters*, 44:4203-6 (2003).
- Pawan et al., "Preliminary Study on the Effects of Fenfluramine Derivative, 'S992' in Man," *British Journal of Pharmacology*, 41(2): 416P-417P (1971).
- Pecherer et al., "The Synthesis of Some 7- and 7,8-Substituted 2,3,4,5-tetrahydro-1H-3-benzazepines," *J. Het. Chem.*, 8(5):779-783 (1971).
- Pecherer et al., "A Novel Synthesis of Aromatic Methoxy and Methylenedioxy Substituted 2,3,4,5-tetrahydro-1H-3-benzazepines," *J. Het. Chem.*, 9:609-16 (1972).
- Perry et al., "Prospective Study of Risk Factors for Development on Non-Insulin Dependent Diabetes in Middle Aged British Men," *BMJ*, 310:560-564 (1995).
- Pfeiffer et al., "Dopaminergic Activity of Substituted 6-Chloro-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines," *J. Med. Chem.*, 25(4):352-8 (1982).
- Piesla et al., "Atypical Antipsychotic-Like Effects of 5-HT2C Agonists," *Schizophrenia Research* 49: 95 (2001).
- Porras, et al., "5-HT2A and 5-HT2C/2B Receptor Subtypes Modulate Dopamine Release Induced in Vivo by Amphetamine and Morphine in Both the Rat Nucleus Accumbens and Striatum," *Neuropsychopharmacology* 26: 311-324 (2002).
- Remington's Pharmaceutical Sciences 17th ed., Mack Publishing Company, Easton Pa.: xv-xvi, 1409-1423 (1985).
- Rosenzweig-Lipson et al., "Vabicaserin: Effects of a Novel 5HT2C Agonist on Medial Prefrontal Cortex Neurotransmission, Cognition and Sensorimotor Gating," 29th ECNP Congress, Vienna, Austria (2007).
- Roth et al., "Anorectic Efficacy of the Fenfluramine/Phentermine Combination in Rats: Additivity or Synergy?" *Eur. J. Pharmacol.*, 373(2-3): 127-34 (1999).
- Rothman, "Treatment of Alcohol and Cocaine Addiction by the Combination of Pemoline and Fenfluramine: A Preliminary Case Series," *Journal of Substance Abuse Treatment*, 12(6):449-53 (1995).
- Rothman et al., "Evidence of Possible Involvement of 5-HT2B Receptors in the Cardiac Valvulopathy Associated with Fenfluramine and Other Serotonergic Medications," *Circulation*, 2836-41 (2000).
- Rowland et al., "Acute Anorectic Effect of Single and Combined Drugs in Mice Using a Non-deprivation Protocol," *Psychopharmacology (Berl)*, 157(2):193-6 (2001).
- Rowland et al., "Anorectic Effect of Dehydroepiandrosterone Combined with Dexfenfluramine or Thionisoxetine," *Eur. J. Pharmacol.*, 419(1):61-4 (2001).
- Rowland et al., "Comparison of Either Norepinephrine-uptake Inhibitors or Phentermine Combined with Serotonergic Agents on Food Intake in Rats," *Psychopharmacology (Berl)*, 149(1):77-83 (2000).
- Rowland et al., "Effects of the Cannabinoid Receptor Antagonist SR 141716, Alone and in Combination with Dexfenfluramine or Naloxone, on Food Intake in Rats," *Psychopharmacology (Berl)*, 159(1):111-6 (2001).
- Schaffner et al., "Preventing Severe Mental Illnesses—New Prospects and Ethical Challenges," *Schizophrenia Research*, 51:3-15 (2001).
- Schladehman et al., "Synthesis of Oxo- and 1-Hydroxy-azobenzocycloalkanes," *J. Chem. Soc. Perkin Trans.*, 2:213-215 (1972).
- Serajuddin et al., "Salt formation to improve drug solubility," *Advanced Drug Delivery Reviews* 59(7):603-616 (2007).
- Silverstone, "Appetite Suppressants: a Review," *Drugs*, 43:6, (1992). Abstract.
- Smith et al., "Discovery and SAR of New Benzazepines as Potent and Selective 5HT2c Receptor Agonists for the Treatment of Obesity," *Bioorganic & Medicinal Chemistry Letters*, 15(5):1467-1470 (2005).

(56)

References Cited

OTHER PUBLICATIONS

Smith, "5-HT_{2C} Receptor Agonists for the Treatment of Obesity," Presentation, Arena Pharmaceuticals, Inc., Jul. 28, 2010, 30 pages.

Smith, "Discovery of Lorcaserin (APD356): A Selective 5HT_{2C} Agonist for the Treatment of Obesity," Presentation, Arena Pharmaceuticals, Inc., (2006).

Smith, et al., "Discovery and Structure—Activity Relationship of (1R)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine (Lorcaserin), a Selective Serotonin 5-HT_{2C} Receptor Agonist for the Treatment of Obesity," *J. Med. Chem.* 51:305-313 (2008).

Sussman et al., "Effects of Nefazodone on Body Weight: A Pooled Analysis of Selective Serotonin Reuptake Inhibitor- and Imipramine-Controlled Trials," *J. Clin. Psychiatry*, 62:4:256-60 (2001).

Tecott et al., "Eating Disorder and Epilepsy in Mice Lacking 5-HT_{2C} Serotonin Receptors," *Nature*, 374:542-546 (1996).

Tietze et al., "Efficient Synthesis of 2, 3, 4, 5-Tetrahydro-1H-3-Benzazepines by Intramolecular Heck Reaction," *Synthesis*, 876-880 (1993).

Tohda et al., "Molecular Pathopharmacology of 5-HT_{2C} Receptors and the RNA Editing in the Brain," *J. Pharma. Science*, 100: 427-432 (2006).

Tsuang et al., "Towards the Prevention of Schizophrenia," *Biol. Psychiatry*, 48:349-356 (2000).

Van Oekelen et al., "5-HT_{2A} and 5-HT_{2C} Receptors and Their Atypical Regulation Properties," *Life Sciences*, 72:2429-2449 (2003).

Vanderlaan et al., "Synthesis and Oxidative Coupling of (±)-3-Sxoreticuline," *J. Org. Chem.*, 50(6):743-7 (1985).

Vink et al., "Risk Factors for Anxiety and Depression in the Elderly: A Review," *J. Affect. Disord.*, 106:29-44 (2008).

Webb, "APD356, A Potential New Treatment for Obesity," Presentation, Arena Pharmaceuticals, Inc., Aug. 11, 2005, 43 pages.

Weinstock et al., "Separation of Potent Central and Renal Dopamine Agonist Activity in Substituted 6-Chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepines," *J. Med. Chem.*, 23(9):973-5 (1980).

Wellman et al., "Synergistic Interactions Between Fenfluramine and Phentermine," *Int. J. Obes.*, 23(7):723-32 (1999).

Wilk, "Exchange Type Reactions Between Oxiranes or Thiiranes and 2-Hydroxyalkyl or 2-Thioalkyl Amines and Sulfides," *Pol. J. Chem.* 62:895 (1988).

Williams, *Chemistry Demystified*, pp. 123, 126 (2003).

Winkler, "Obesity and Hemostasis" *Archives of Gynecology & Obst.* 261(1):25-29 (1997).

Wise, "Addiction Becomes a Brain Disease," *Neuron*, 26: 27-33 (2000).

Wisner et al., "Postpartum Depression," *N. Engl. J. Med.*, 347(3):194-199 (2002).

Woods et al., "Annual Report: Evaluation of New Compounds for Opioid Activity," National Institute on Drug Abuse, Proceedings of the 41st Annual Scientific Meeting pp. 356-401 (1979).

Wu et al., "Amino Diol Based Asymmetric Syntheses of a Fused Benzazepine as a Selective D₁ Dopamine Receptor," *Organic Process Research & Development*, 1(5):359-64 (1997).

Yasuda et al., "A Novel and Stereoselective Synthesis of (±)-Cephalotaxine and its Analogue," *Tetrahedron Letters*, 27(18):2023-6 (1986).

Yonemitsu et al., "Photolysis of N-Chloroacetyl-O-methyl-L-tyrosine to an Azaazulene," *J. Am. Chem. Soc.*, 89(4): 1039-40 (1967).

Yonemitsu et al., "Photocyclization of Pharmacodynamic Amines. IV. Novel Heterocycles from N-chloroacetyl-3,4-dimethoxyphenethylamine," *J. Am. Chem. Soc.*, 92(19):5686-90 (1970).

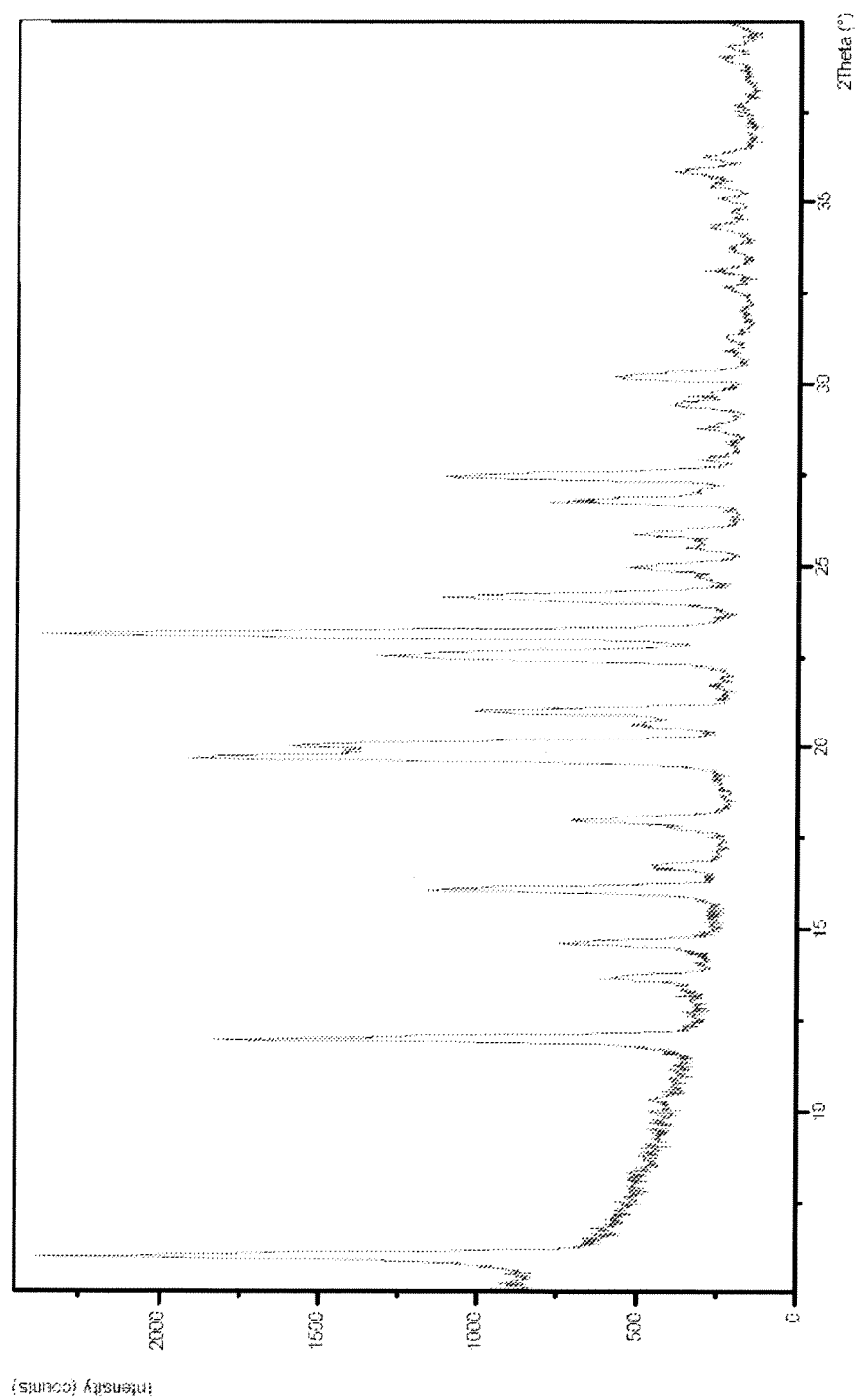
Yonemitsu et al., "Photocyclization of Pharmacodynamic Amines. II. X-Ray Analysis of a Noncentrosymmetric Tetracyclic Indole," *J. Am. Chem. Soc.*, 90(23):6522-3 (1968).

Yonemitsu et al., "Photocyclizations of Tyrosines, Tyramines, Catecholamines, and Normescaline," *J. Am. Chem. Soc.*, 90(3):776-84 (1968).

Yoshinaga et al., "Prevention of Mildly Overweight Children from Development of More Overweight Condition," *Prevention Medicine*, 38:172-174 (2004).

Zhang et al., "Convolutamines A-E, Novel β-Phenylethylamine Alkaloids from Marine Bryozoan *Amathia convolute*," *Chem. Lett.*, 12:2271-2274 (1994).

* cited by examiner

PXRD of Compound 1 Hemi-edisylate Salt, Form I**Figure 1**

DSC and TGA of Compound 1 Hemi-edisylate Salt, Form I

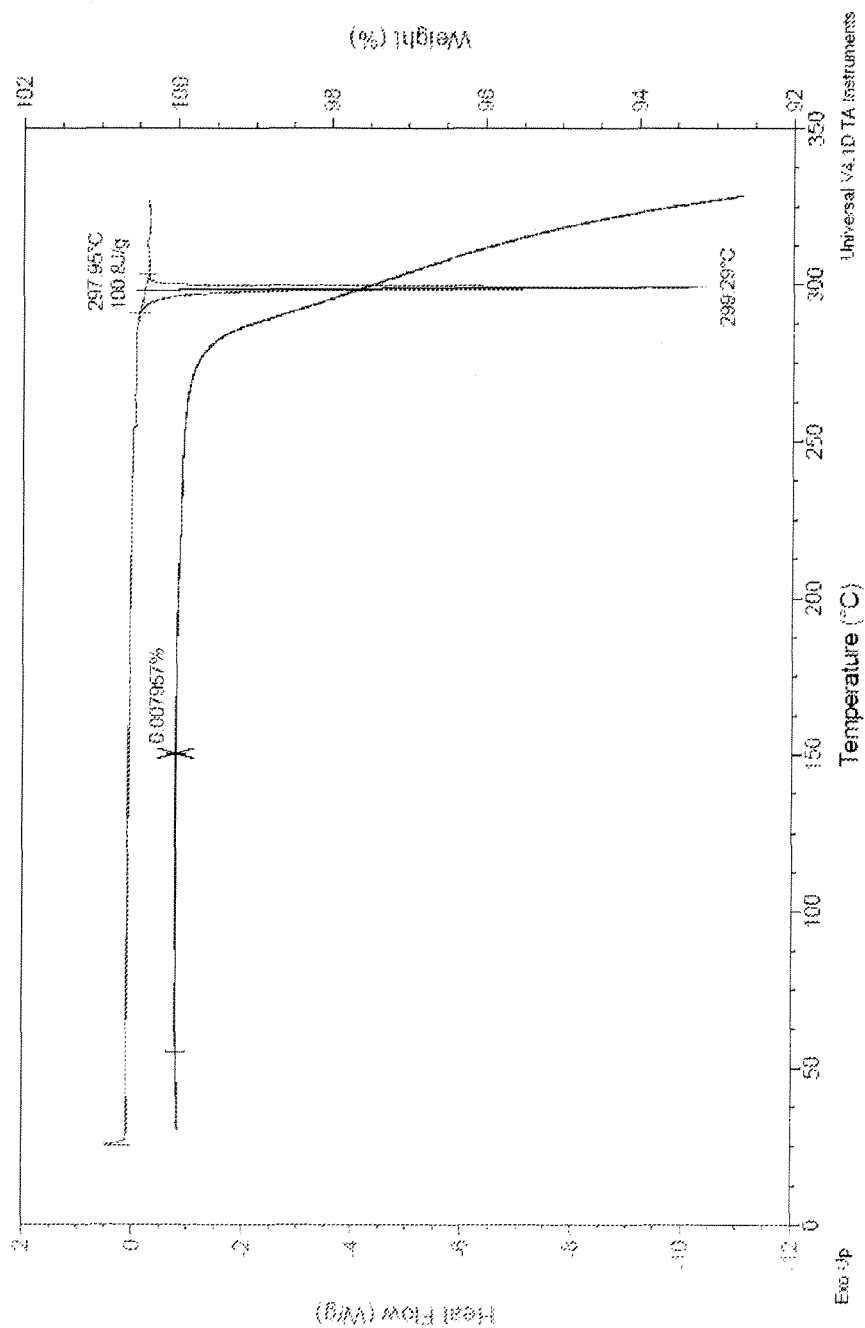


Figure 2

DMS of Compound 1 Hemi-edisylate Salt, Form I

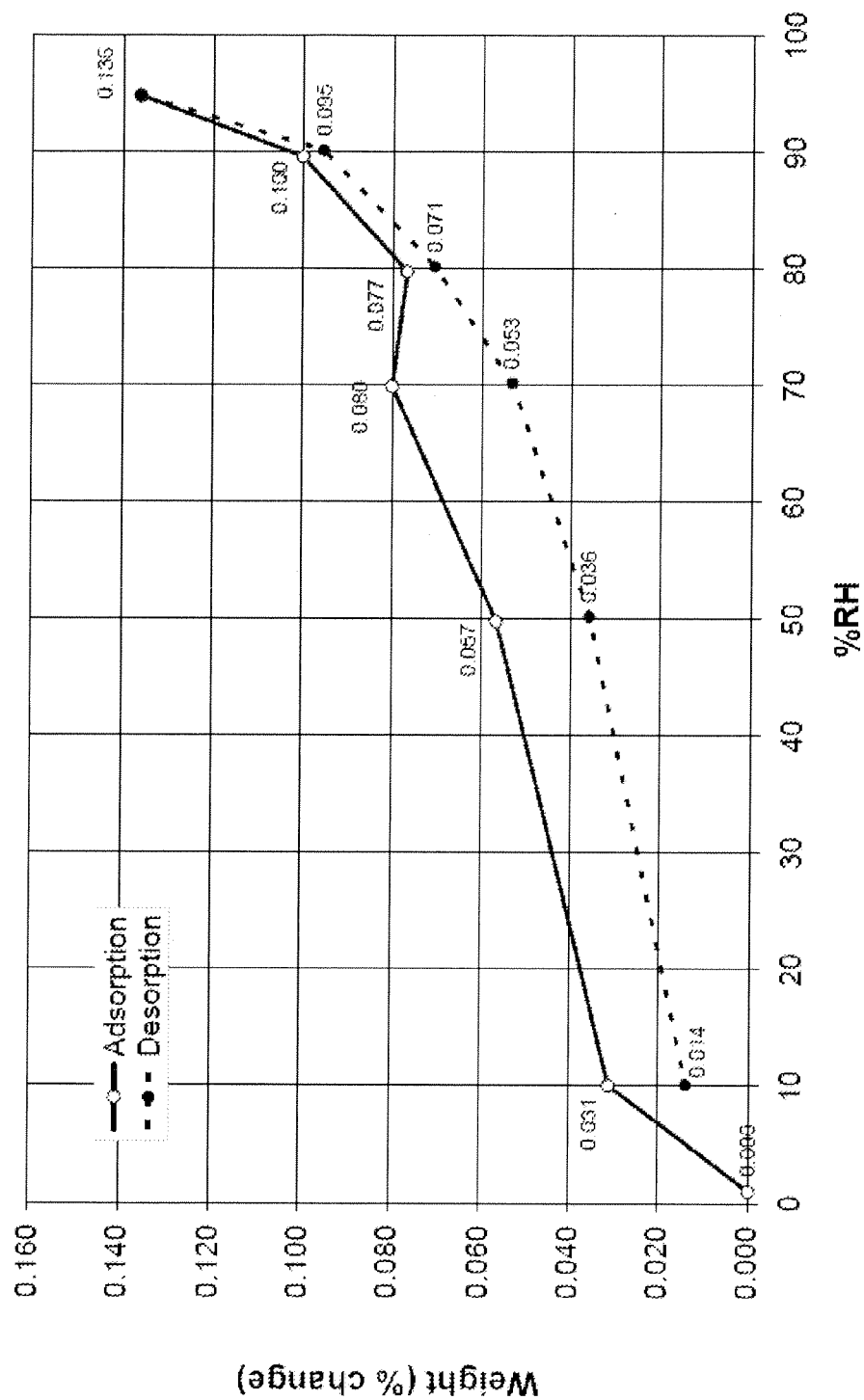


Figure 3

PXRD of Compound 1 Phosphate Salt, Form I

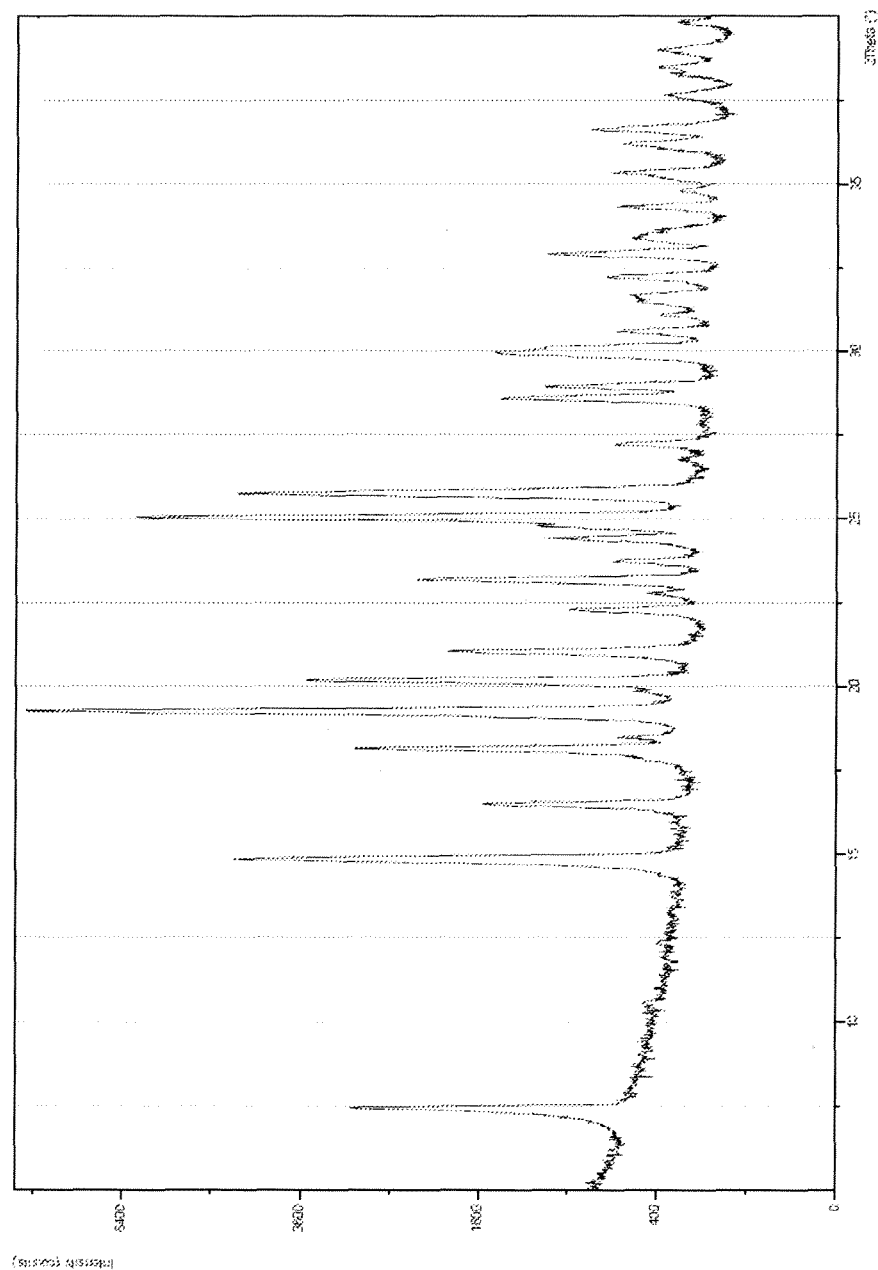


Figure 4

DSC and TGA of Compound 1 Phosphate Salt, Form I

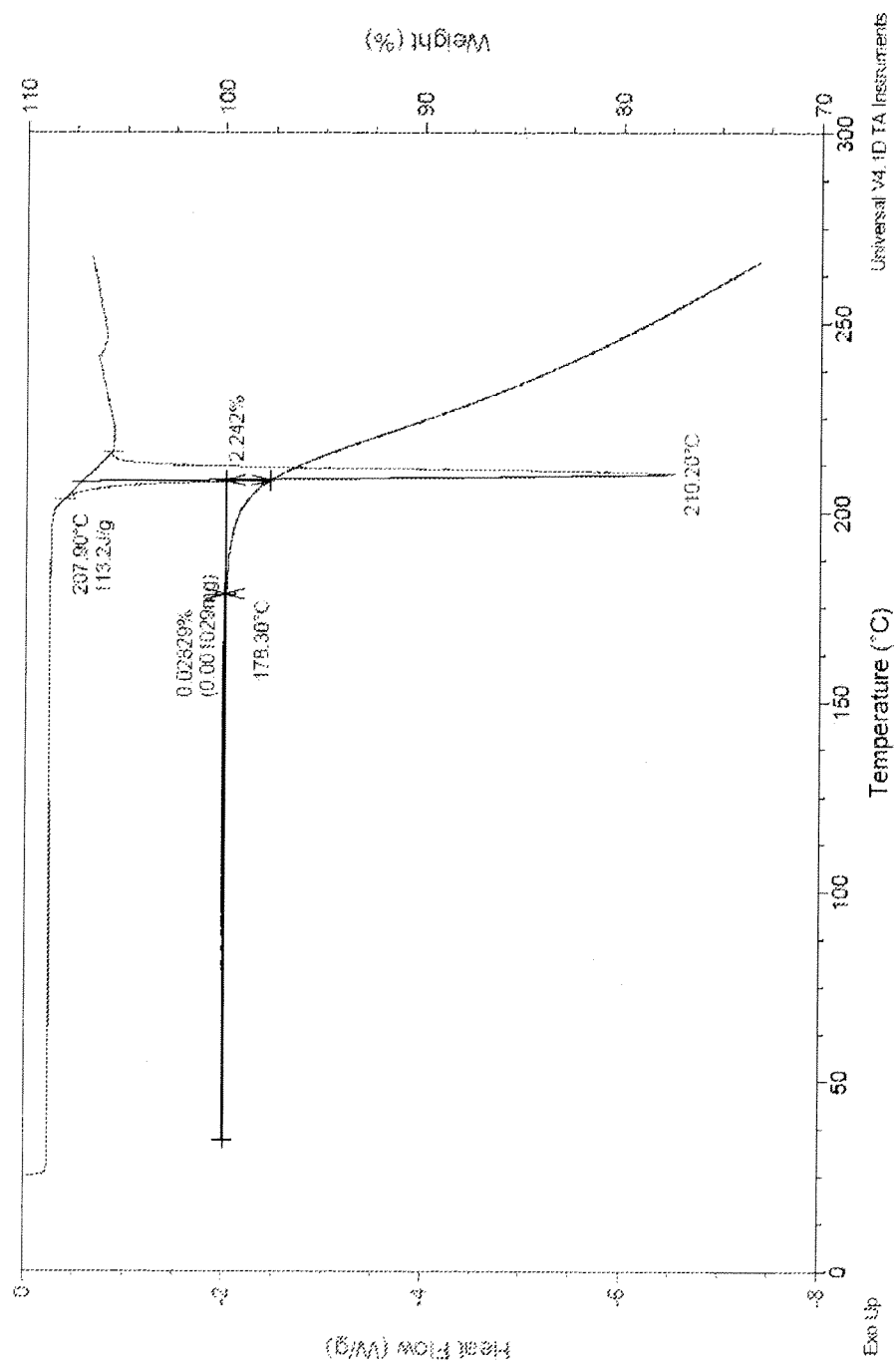


Figure 5

DMS of Compound 1 Phosphate Salt, Form I

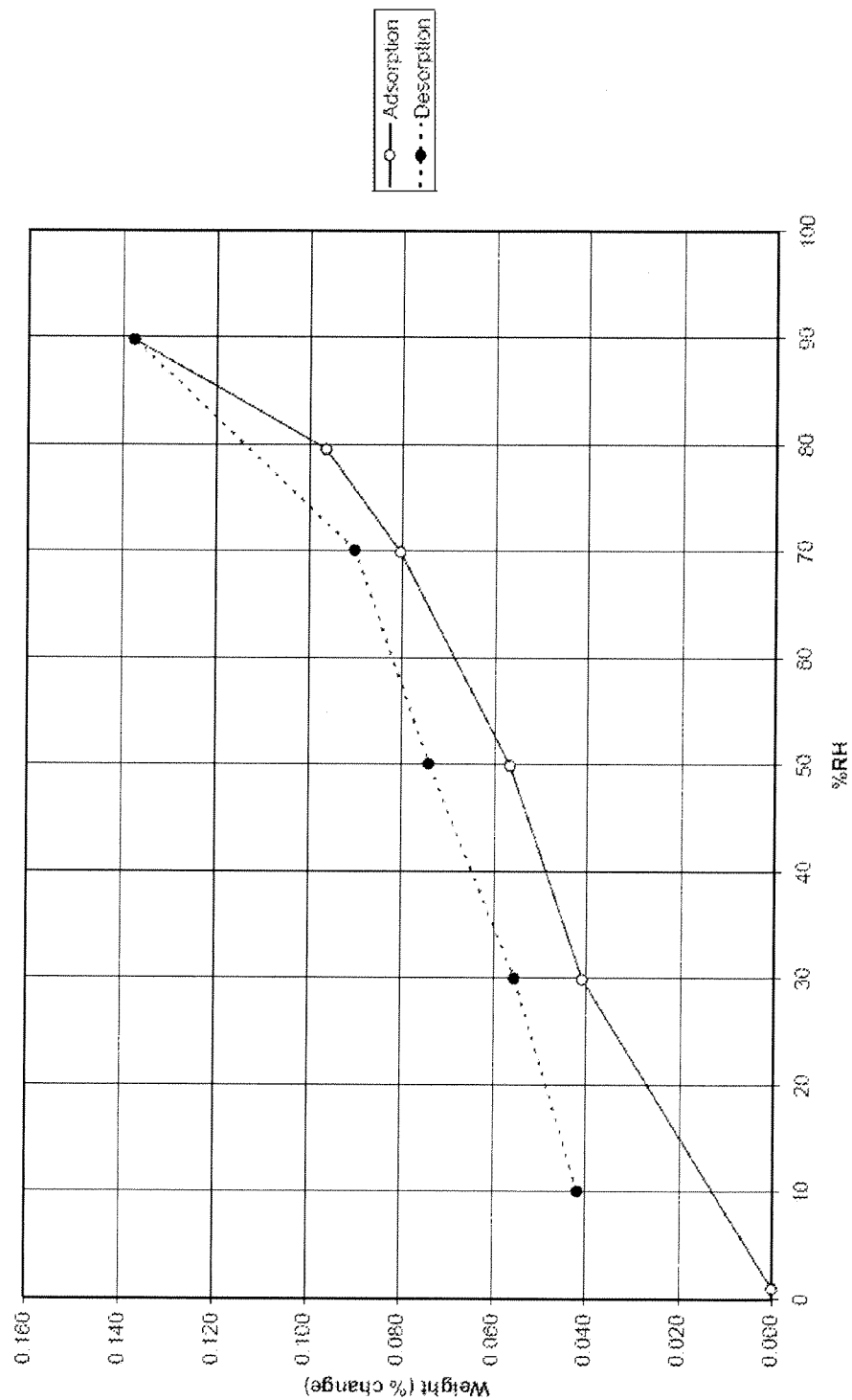


Figure 6

PXRD of Compound 1 Citrate Salt Hemihydrate, Form I

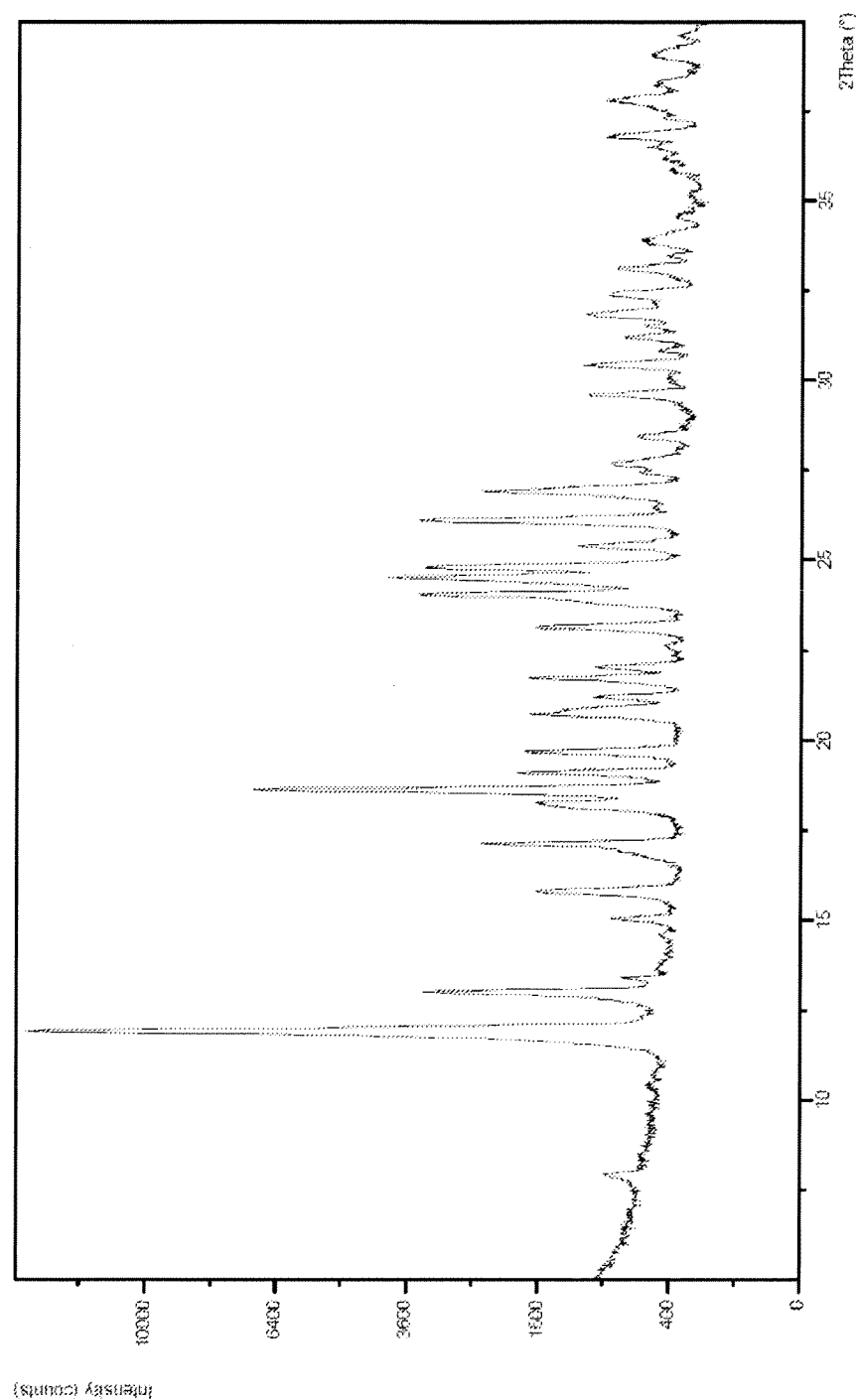
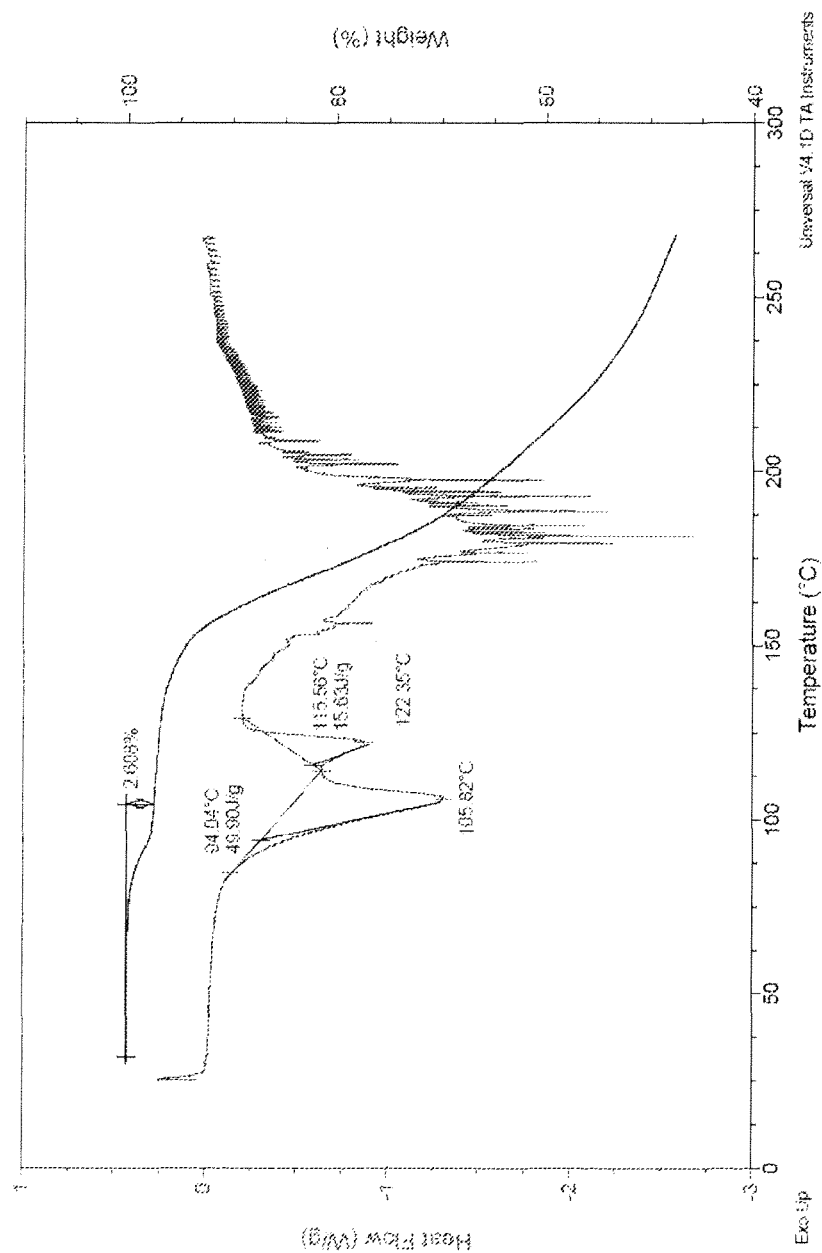


Figure 7

DSC and TGA of Compound 1 Citrate Salt Hemihydrate Salt, Form I**Figure 8**

DMS of Compound 1 Citrate Salt Hemihydrate Salt, Form I

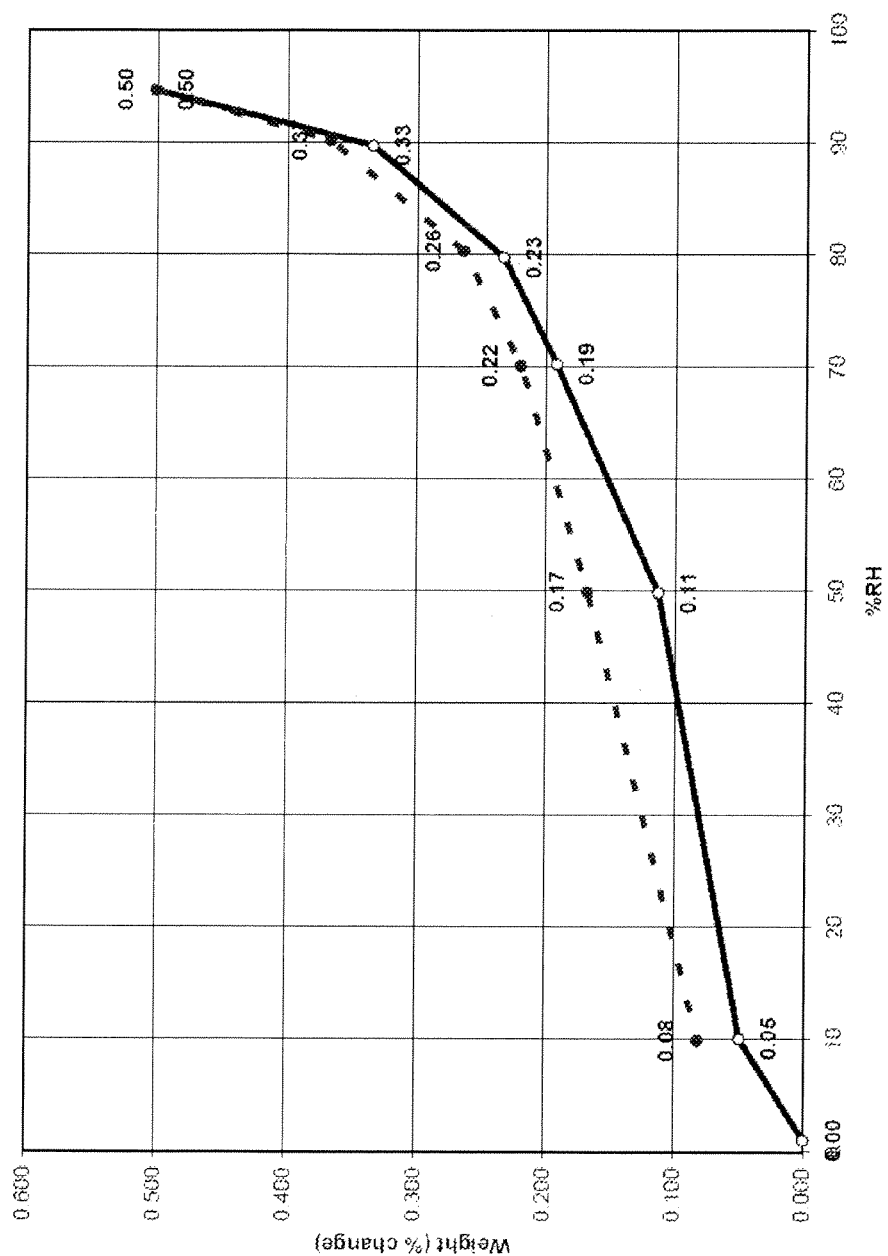


Figure 9

PXRD of Compound 1 Hemi-oxalate Salt, Form I

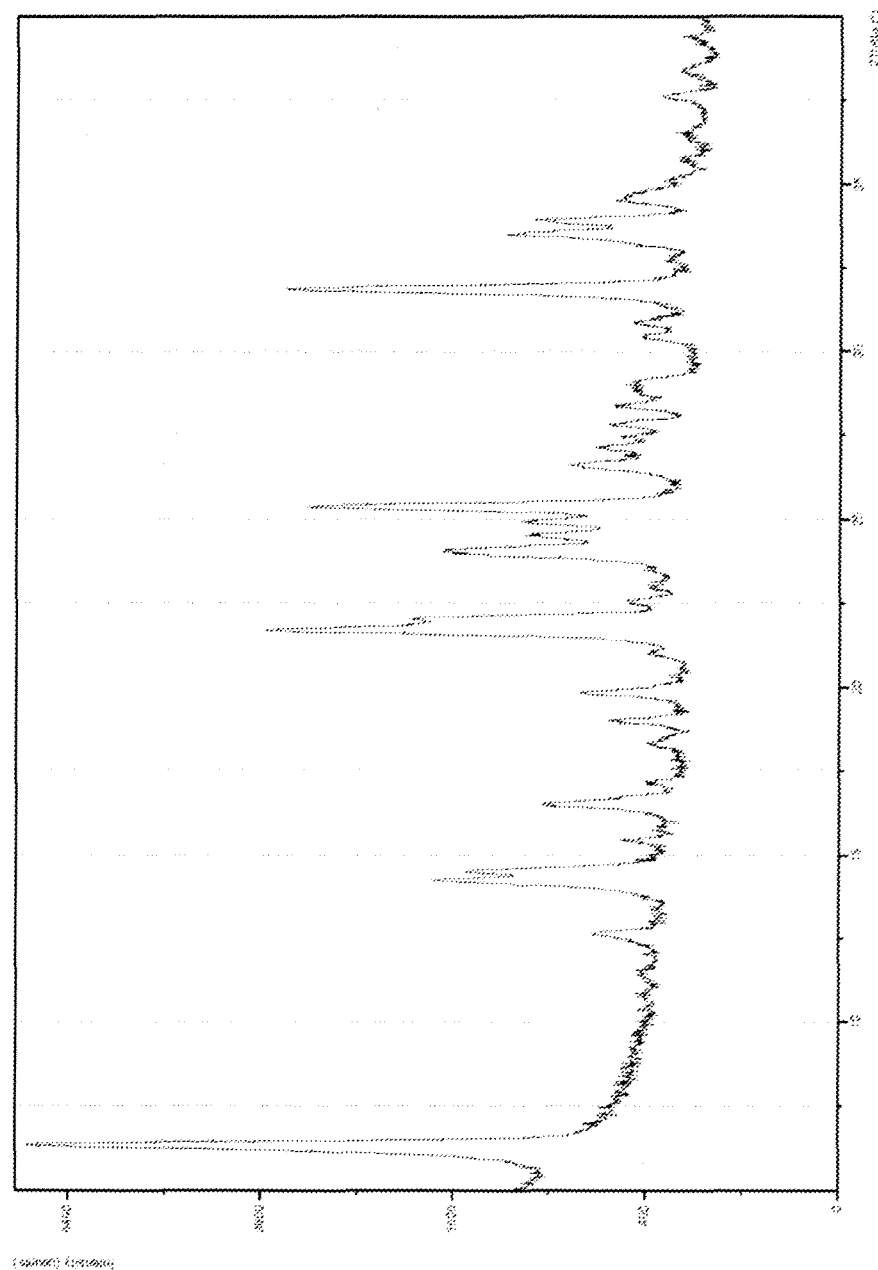
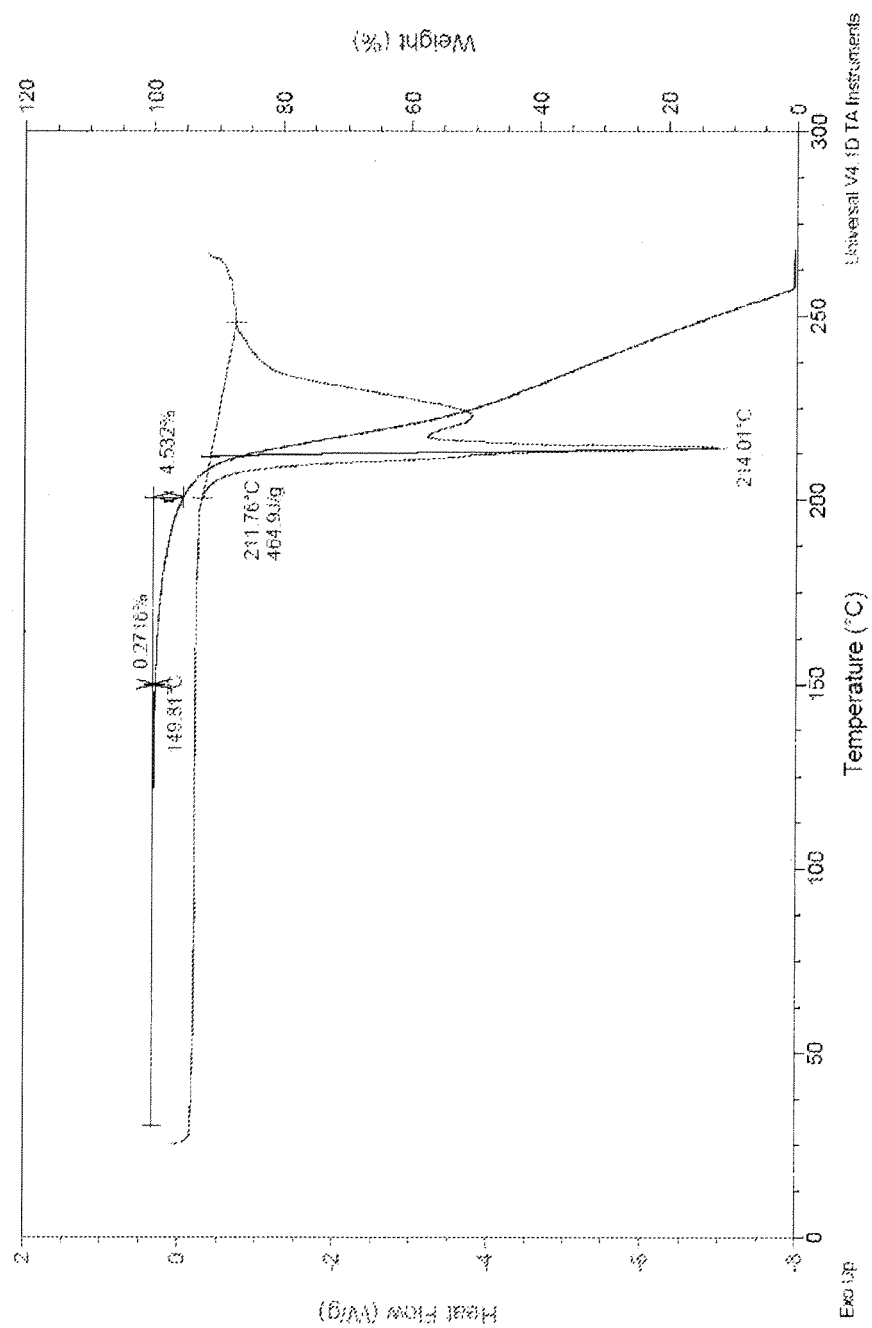


Figure 10

DSC and TGA of Compound 1 Hemi-oxalate Salt, Form I



Universal V4 TD TA Instruments

Figure 11

DMS of Compound 1 Hemi-oxalate Salt, Form I

Adsorption/Desorption Isotherm

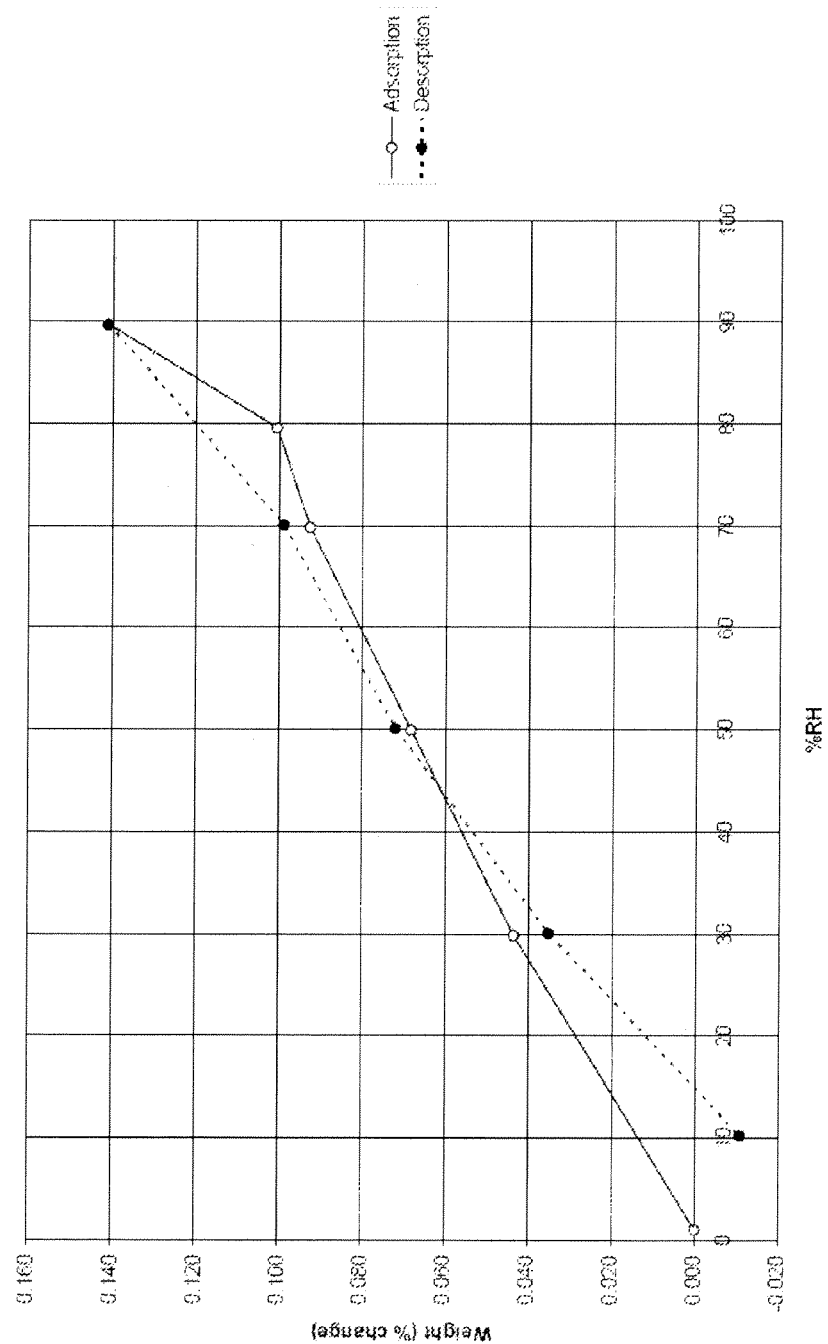


Figure 12

PXRD of Compound 1 Succinate Salt, Form I

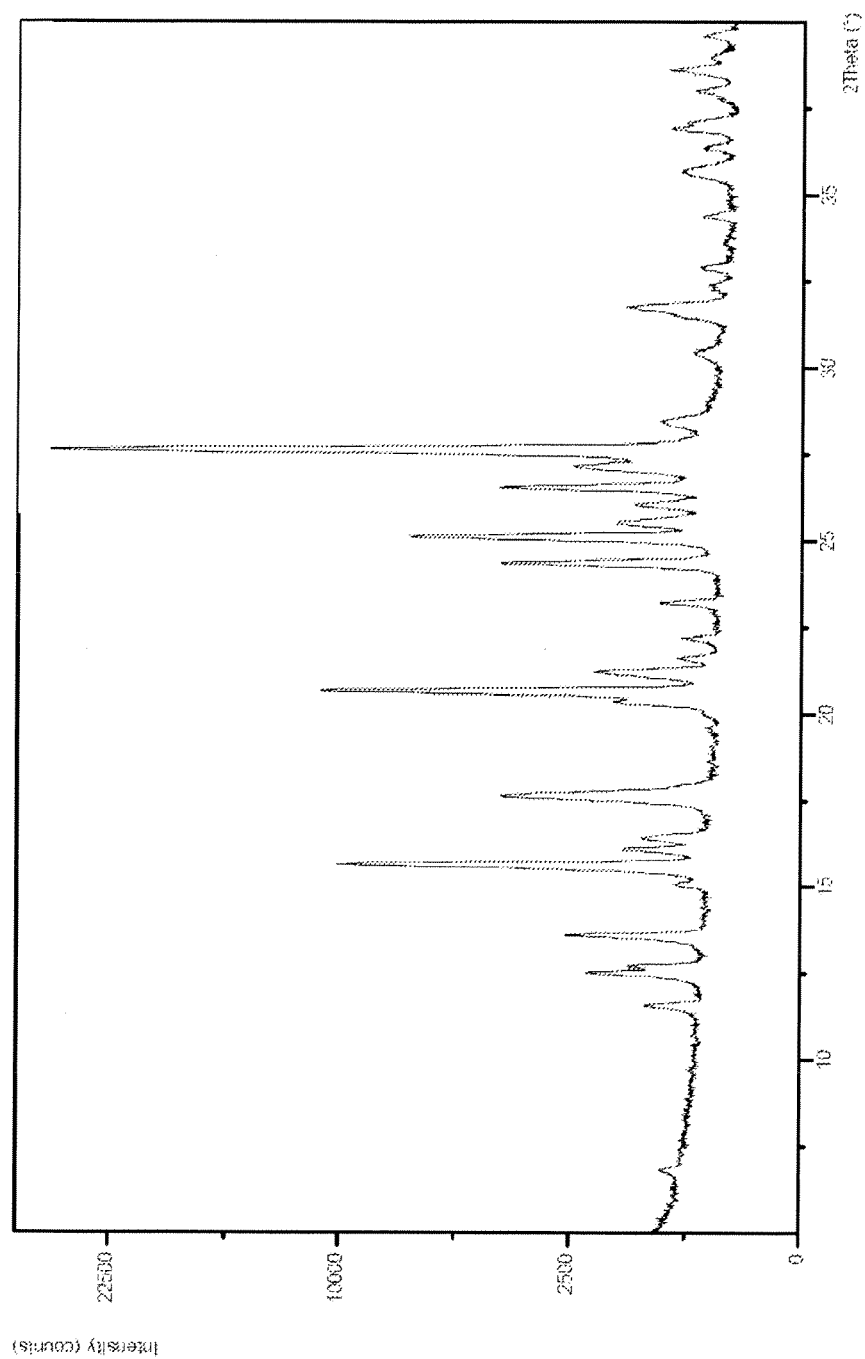


Figure 13

DSC and TGA of Compound 1 Succinate Salt, Form I

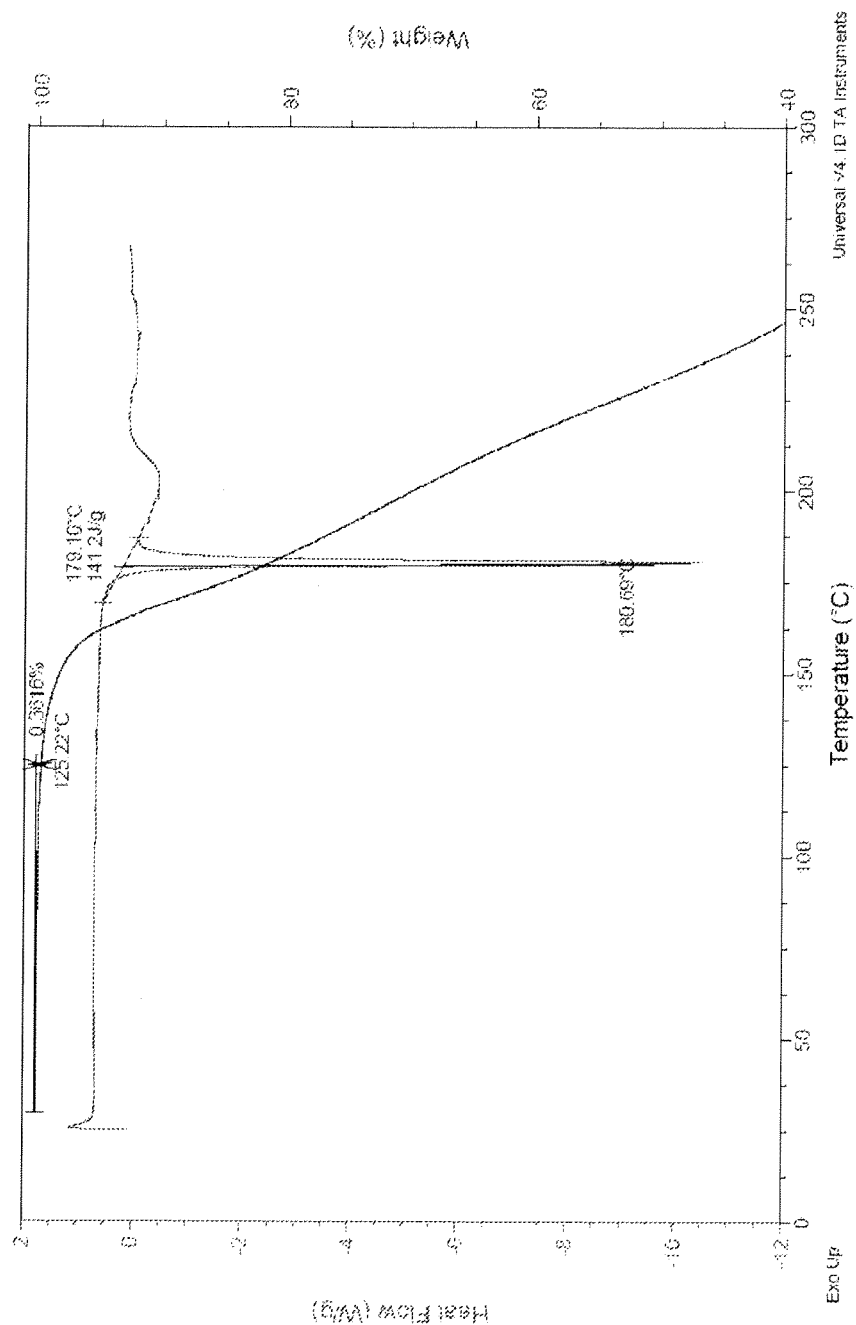


Figure 14

DMS of Compound 1 Succinate Salt, Form I

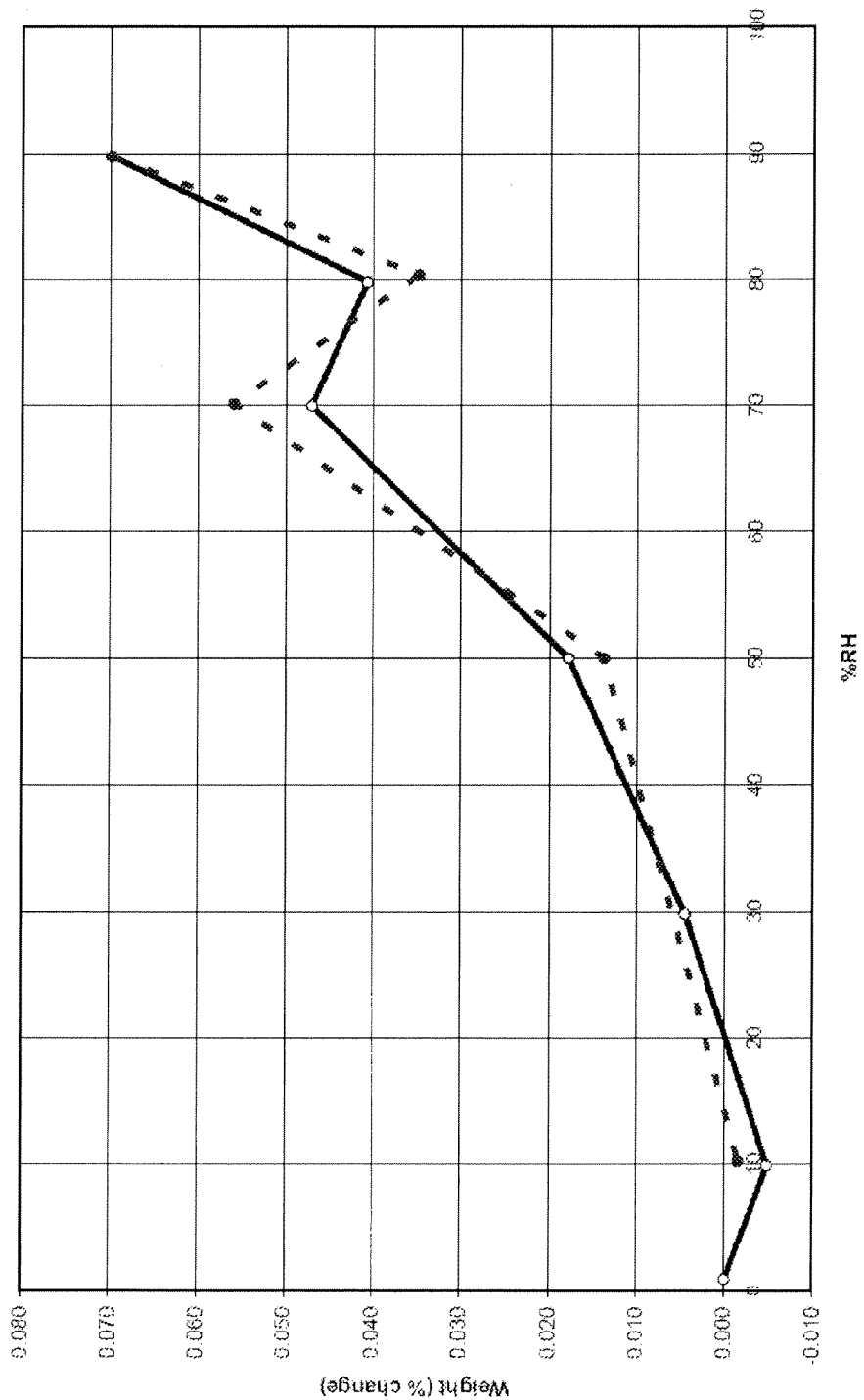


Figure 15

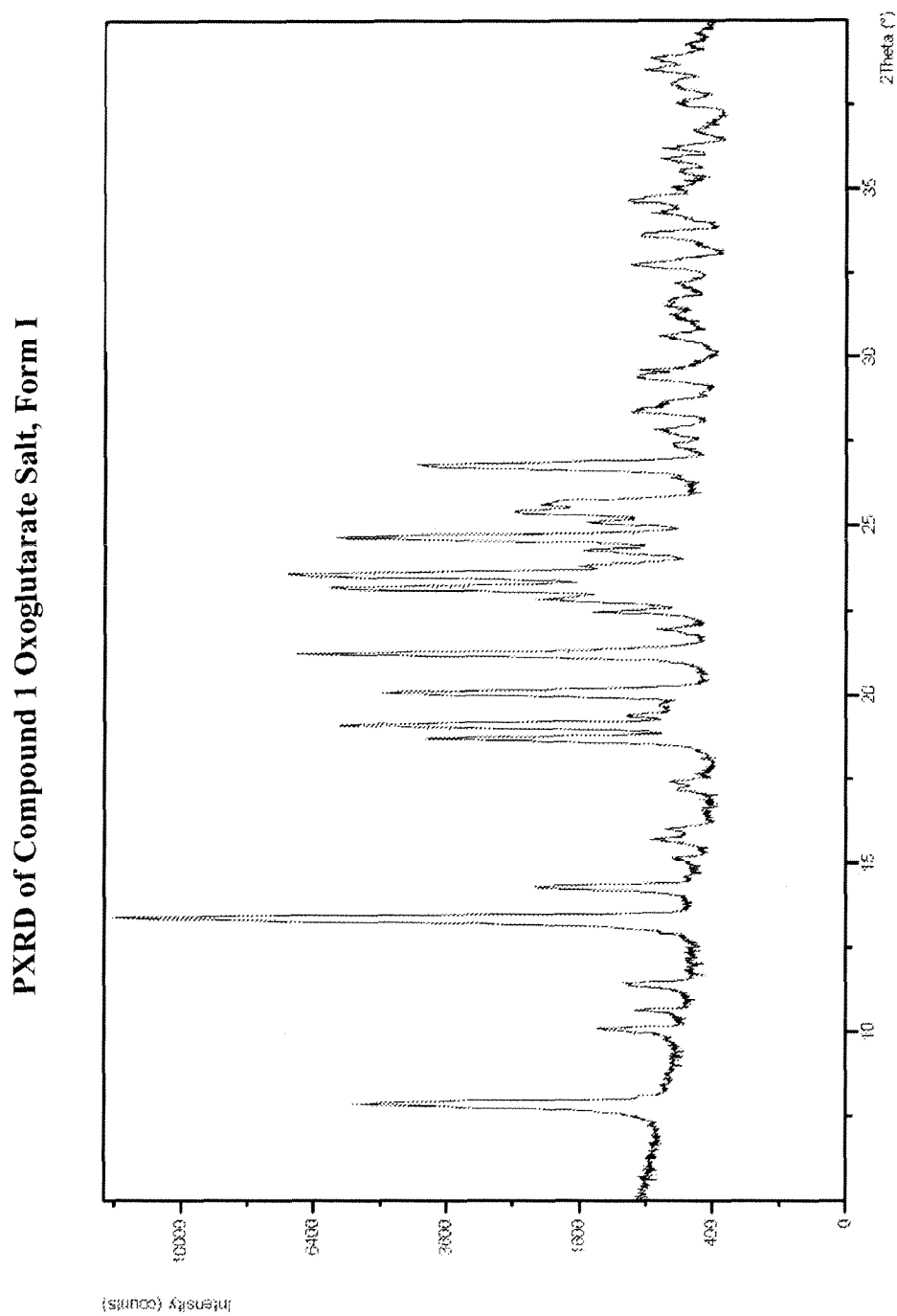
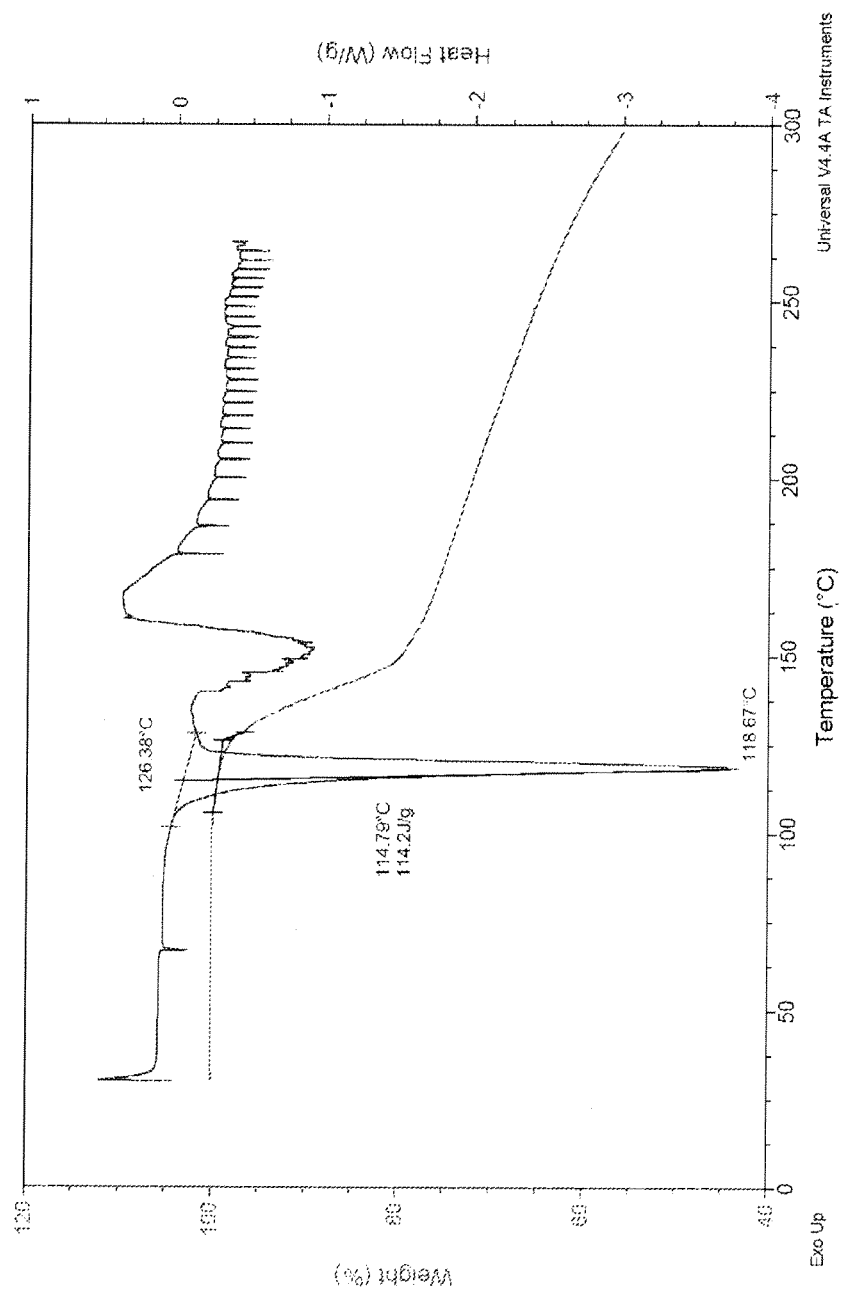


Figure 16

DSC and TGA of Compound 1 Oxoglutarate Salt, Form I**Figure 17**

DMS of Compound 1 Oxoglutarate Salt, Form I

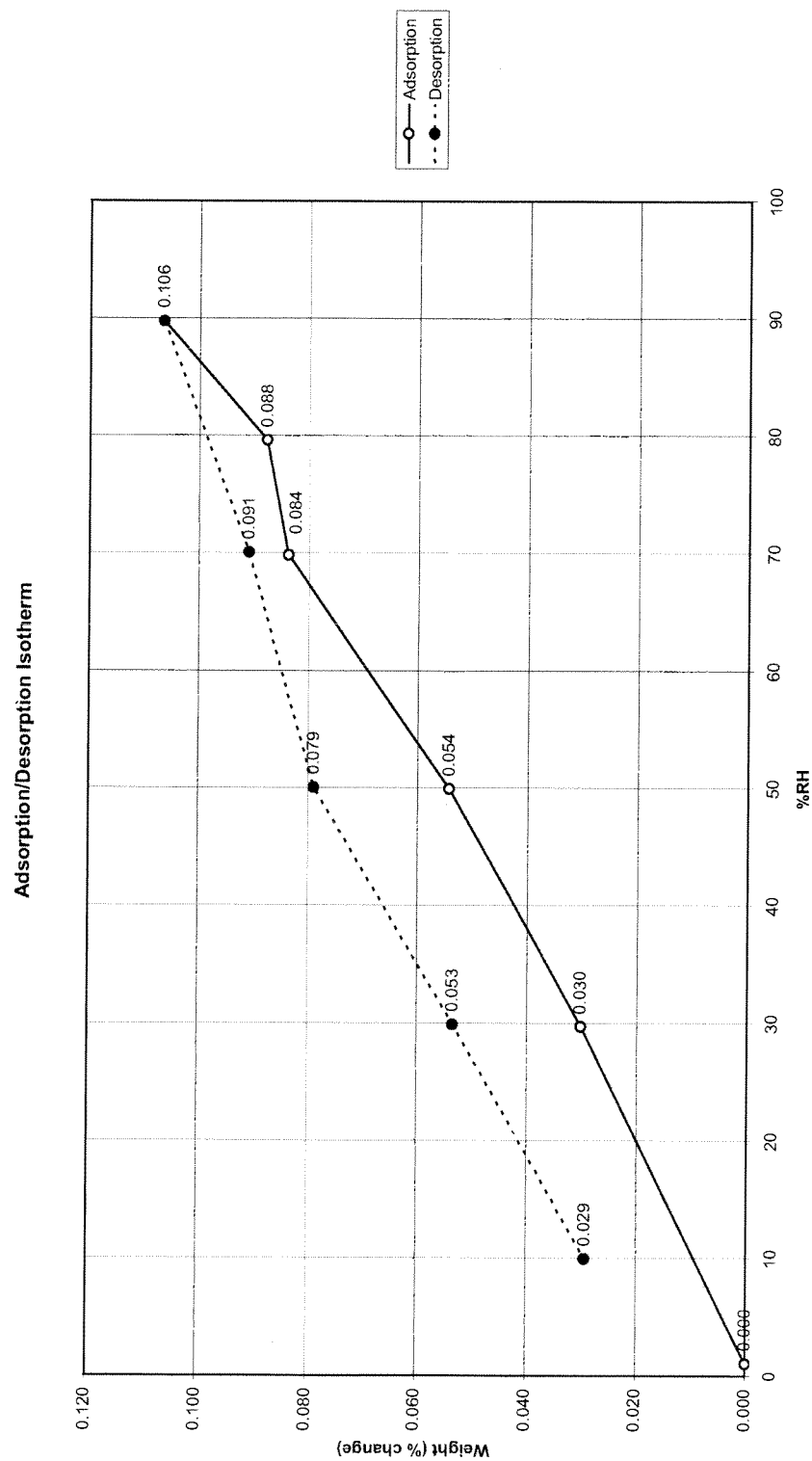


Figure 18

PXRD of Compound 1 Oxoglutarate Salt Solvate, Form I

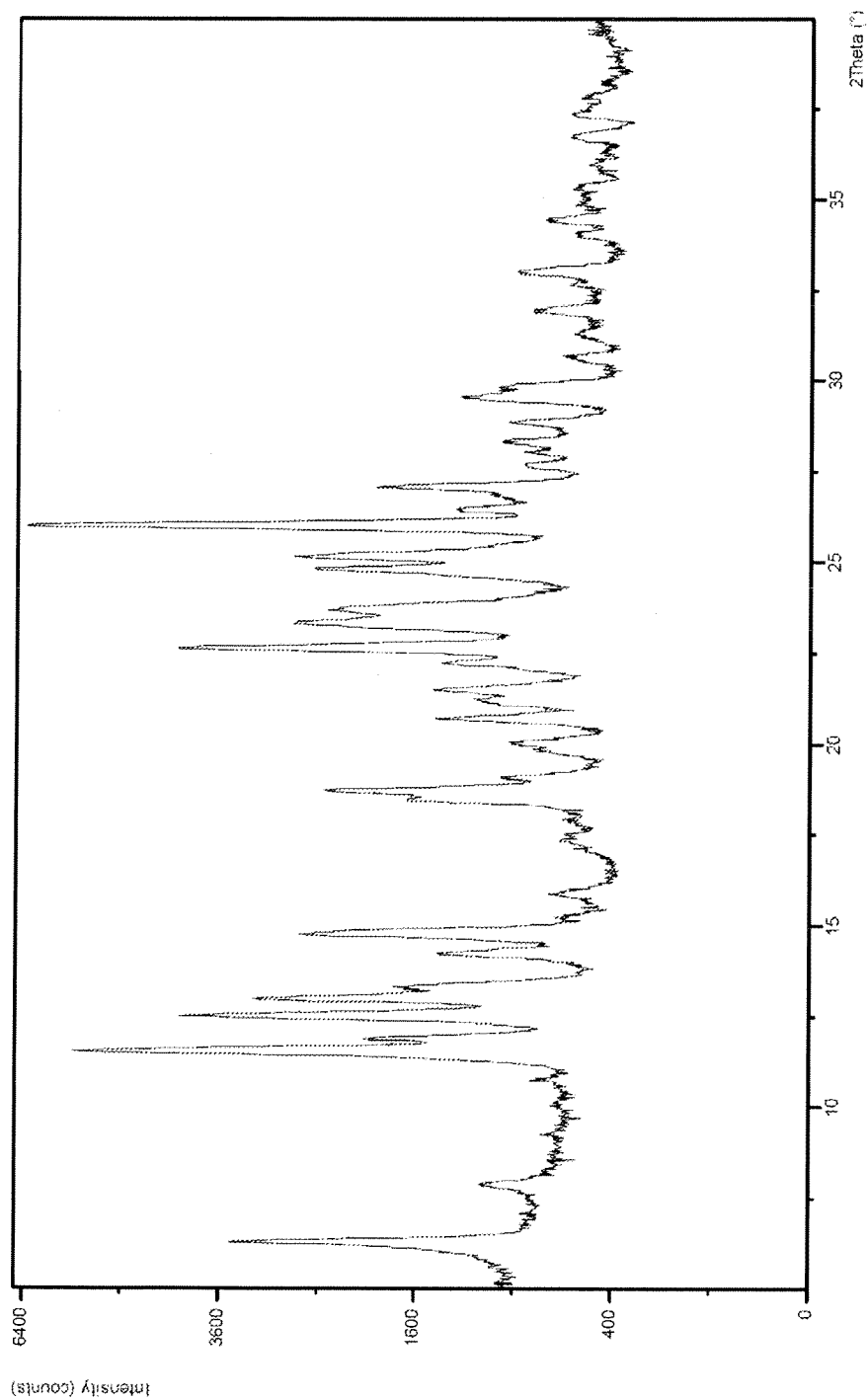
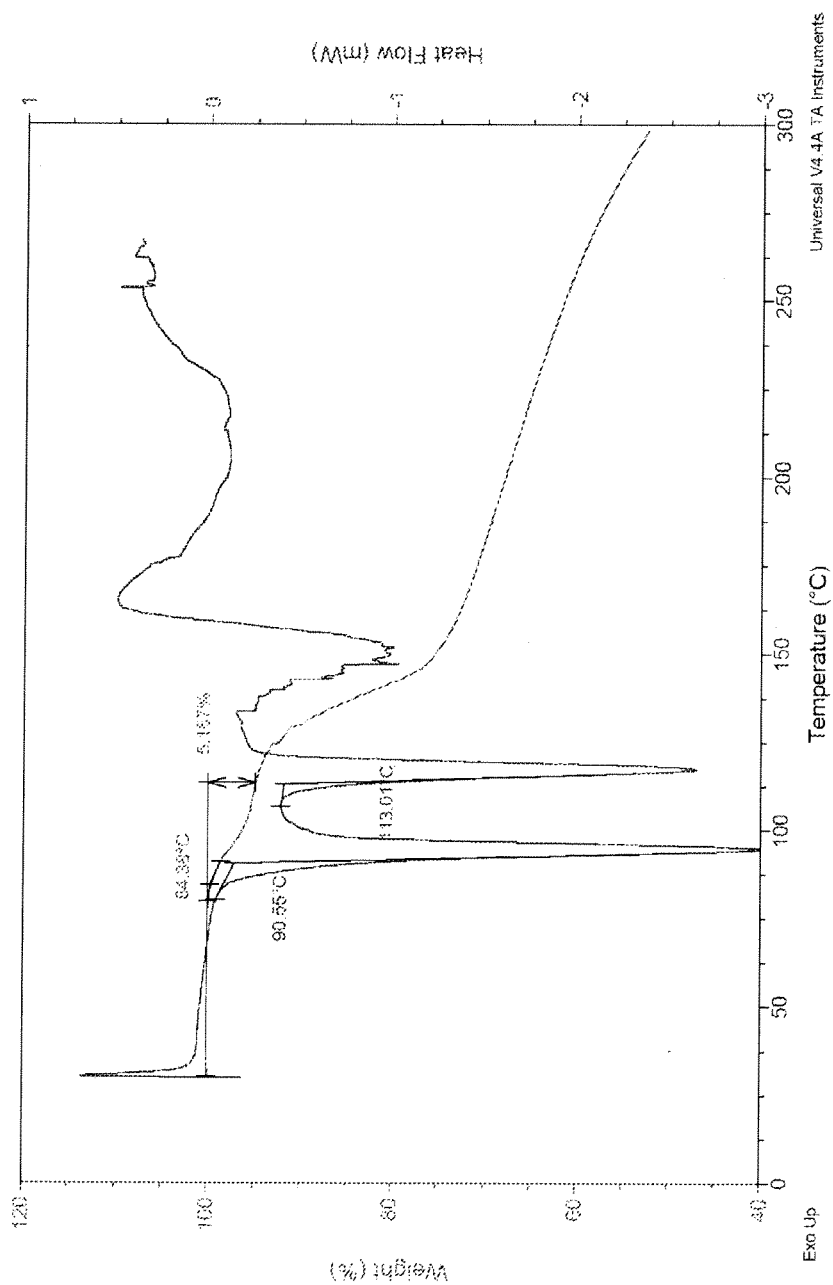


Figure 19

DSC and TGA of Compound 1 Oxoglutarate Salt Solvate, Form I**Figure 20**

DMS of Compound 1 Oxoglutarate Salt Solvate, Form I

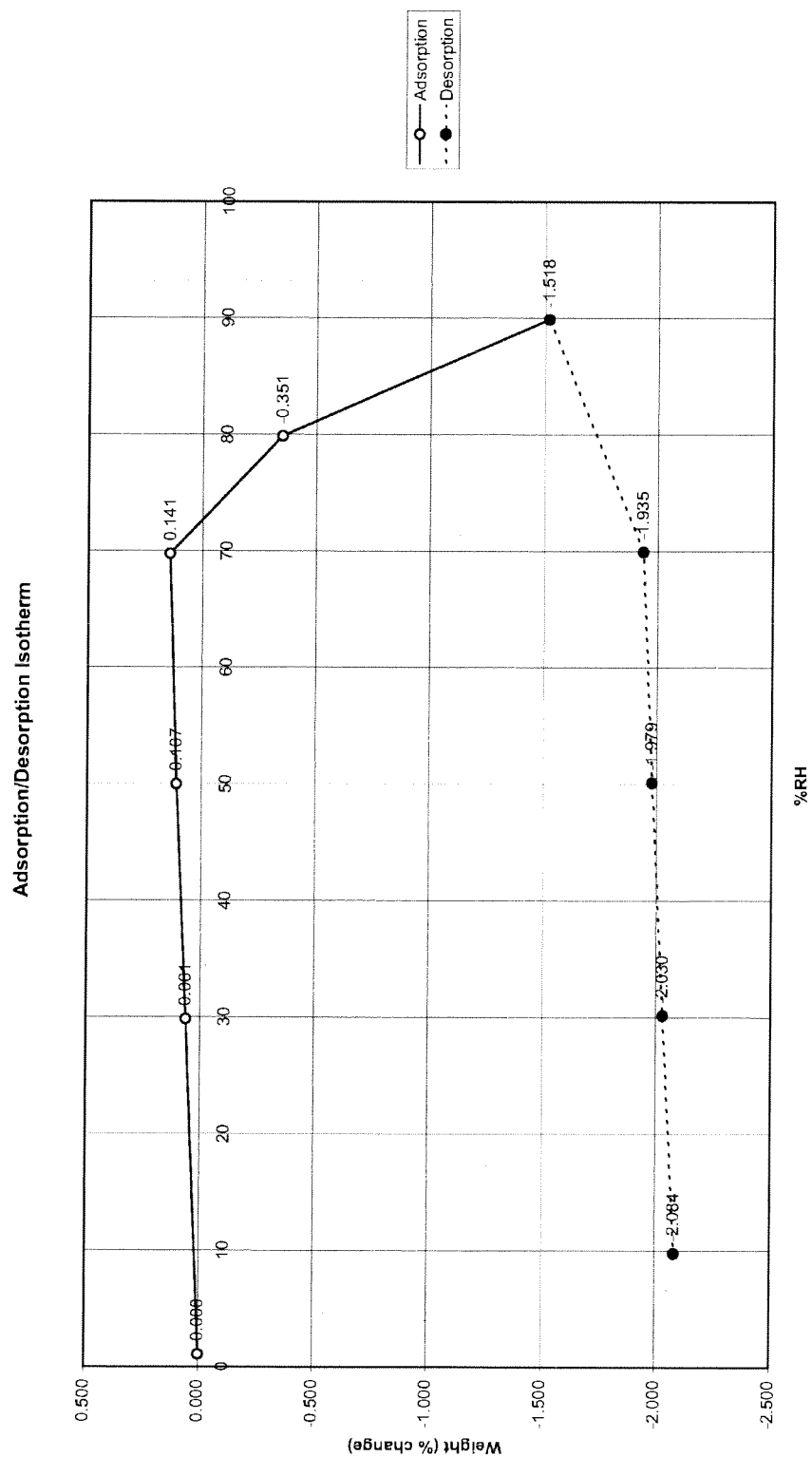


Figure 21

NON-HYGROSCOPIC SALTS OF 5-HT_{2C} AGONISTS

This application is a 35 USC 371 National Stage Entry of PCT/US2011/049960 filed Aug. 31, 2011, and claims the benefit of U.S. Provisional Application No. 61/402,611 filed Sep. 1, 2010, each of which is incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

The present invention relates to salts of the 5-HT_{2C}-receptor agonist (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and dosage forms comprising them that are useful for, inter alia, weight management.

BACKGROUND OF THE INVENTION

Obesity is a life-threatening disorder in which there is an increased risk of morbidity and mortality arising from concomitant diseases such as type II diabetes, hypertension, stroke, cancer and gallbladder disease.

Obesity is now a major healthcare issue in the Western World and increasingly in some third world countries. The increase in numbers of obese people is due largely to the increasing preference for high fat content foods but also the decrease in activity in most people's lives. Currently about 30% of the population of the USA is now considered obese.

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m²). Thus, the units of BMI are kg/m² and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m², and obesity as a BMI greater than 30 kg/m² (see table below).

Classification of Weight by Body Mass Index (BMI)

BMI	CLASSIFICATION
<18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Obesity (Class I)
35.0-39.9	Obesity (Class II)
>40	Extreme Obesity (Class III)

As the BMI increases there is an increased risk of death from a variety of causes that are independent of other risk factors. The most common diseases associated with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. The strength of the link between obesity and specific conditions varies. One of the strongest is the link with type 2 diabetes. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women (Seidell, *Semin Vasc Med*, 5:3-14 (2005)). Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

There are problems however with the BMI definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for

this, obesity can also be defined on the basis of body fat content: greater than 25% in males and greater than 30% in females.

Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atherosclerotic disease, and cardiac insufficiency are at the forefront of the cardiovascular complications induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents would decrease by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for diabetes and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of obesity (Perry, I. J., et al., *BMJ* 310, 560-564 (1995)).

Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.

The first line of treatment is to offer diet and life style advice to patients such as reducing the fat content of their diet and increasing their physical activity. However, many patients find this difficult and need additional help from drug therapy to maintain results from these efforts.

Most currently marketed products have been unsuccessful as treatments for obesity because of a lack of efficacy or unacceptable side-effect profiles. The most successful drug so far was the indirectly acting 5-hydroxytryptamine (5-HT) agonist d-fenfluramine (ReduxTM) but reports of cardiac valve defects in up to one third of patients led to its withdrawal by the FDA in 1998.

In addition, two drugs have been launched in the USA and Europe: Orlistat (XenicalTM) a drug that prevents absorption of fat by the inhibition of pancreatic lipase, and Sibutramine (ReductilTM), a 5-HT/noradrenaline re-uptake inhibitor. However, side effects associated with these products may limit their long-term utility. Treatment with XenicalTM is reported to induce gastrointestinal distress in some patients, while Sibutramine has been associated with raised blood pressure in some patients.

Serotonin (5-HT) neurotransmission plays an important role in numerous physiological processes both in physical and in psychiatric disorders. 5-HT has been implicated in the regulation of feeding behavior. 5-HT is believed to work by inducing a feeling of satiety, such that a subject with enhanced 5-HT stops eating earlier and fewer calories are consumed. It has been shown that a stimulatory action of 5-HT on the 5-HT_{2C} receptor plays an important role in the control of eating and in the anti-obesity effect of d-fenfluramine. As the 5-HT_{2C} receptor is expressed in high density in the brain (notably in the limbic structures, extrapyramidal pathways, thalamus and hypothalamus i.e. PVN and DMH, and predominantly in the choroid plexus) and is expressed in

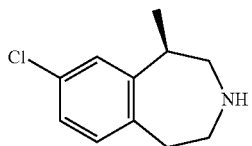
3

low density or is absent in peripheral tissues, a selective 5-HT_{2C} receptor agonist can be a more effective and safe anti-obesity agent. Also, 5-HT_{2C} knockout mice are overweight with cognitive impairment and susceptibility to seizure.

It is believed that the 5-HT_{2C} receptor may play a role in obsessive compulsive disorder, some forms of depression, and epilepsy. Accordingly, agonists can have anti-panic properties, and properties useful for the treatment of sexual dysfunction.

In sum, the 5-HT_{2C} receptor is a receptor target for the treatment of obesity and psychiatric disorders, and it can be seen that there is a need for selective 5-HT_{2C} agonists which safely decrease food intake and body weight.

The salts and formulations of the present invention comprise the selective 5-HT_{2C}-receptor agonist (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Compound 1), and are useful for, inter alia, weight management, including weight loss and the maintenance of weight loss. Compound 1 is disclosed in PCT patent publication WO2003/086303, which is incorporated herein by reference in its entirety.



Various synthetic routes to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, its related salts, enantiomers, crystalline forms, and intermediates, have been reported in PCT publications, WO 2005/019179, WO 2006/069363, WO 2007/120517, WO 2008/070111, WO 2009/111004, and in U.S. provisional application 61/396,752 each of which is incorporated herein by reference in its entirety.

Combinations of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine with other agents, including without limitation, phentermine, and uses of such combinations in therapy are described in WO 2006/071740, which is incorporated herein by reference in its entirety.

The following United States provisional applications are related to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine: 61/402,578; 61/403,143; 61/402,580; 61/402,628; 61/403,149; 61/402,589; 61/402,611; 61/402,565; 61/403,185; each of which is incorporated herein by reference in its entirety.

The following applications are related to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and have the same filing date as the subject application, a PCT application which claims priority to U.S. provisional applications 61/402,578 and 61/403,143, a PCT application which claims priority to U.S. provisional application 61/402,580; a PCT application which claims priority to U.S. provisional applications 61/402,628 and 61/403,149; a PCT application which claims priority to U.S. provisional application 61/402,589; and a PCT application which claims priority to U.S. provisional applications 61/402,565 and 61/403,185; each of which is incorporated herein by reference in its entirety.

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (lorcaserin hydrochloride) is an agonist of the 5-HT_{2C} receptor and shows effectiveness at reducing obesity in animal models and humans. In December 2009, Arena Pharmaceuticals submitted a New Drug Application,

4

or NDA, for lorcaserin to the FDA. The NDA submission is based on an extensive data package from lorcaserin's clinical development program that includes 18 clinical trials totaling 8,576 patients. The pivotal phase 3 clinical trial program evaluated nearly 7,200 patients treated for up to two years, and showed that lorcaserin consistently produced significant weight loss with excellent tolerability. About two-thirds of patients achieved at least 5% weight loss and over one-third achieved at least 10% weight loss. On average, patients lost 17 to 18 pounds or about 8% of their weight. Secondary endpoints, including body composition, lipids, cardiovascular risk factors and glycemic parameters improved compared to placebo. In addition, heart rate and blood pressure went down. Lorcaserin did not increase the risk of cardiac valvulopathy. Lorcaserin improved quality of life, and there was no signal for depression or suicidal ideation. The only adverse event that exceeded the placebo rate by 5% was generally mild or moderate, transient headache. Based on a normal BMI of 25, patients in the first phase 3 trial lost about one-third of their excess body weight. The average weight loss was 35 pounds or 16% of body weight for the top quartile of patients in the second phase 3 trial.

An immediate-release film-coated 10-mg tablet was developed for the phase 3 clinical trials and commercial launch of lorcaserin, but there remains a need for alternative formulations for oral use. These include formulations characterized by their suitable flowing properties, tablettability, and stability to moisture.

In view of the growing demand for compounds useful in the treatment of disorders related to the 5-HT_{2C} receptor, (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine has emerged as an important new compound. Accordingly, new formulations of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, which are non-hygroscopic and show good solid-state stability under humid conditions are needed. The salts and processes described herein help meet these and other needs.

SUMMARY OF THE INVENTION

A priori, it is difficult to predict with confidence which salts of a particular drug will be solid, stable, and readily isolable. A fortiori, the hygroscopicity of such salts cannot be predicted with accuracy and must instead be determined empirically. In the course of preparing the salts of the present invention, many counterions commonly used in the pharmaceutical industry (see e.g. Berge, et al., *Journal of Pharmaceutical Sciences*, 66:1-19 (1977)) were investigated. Acetate, DL-lactate, ascorbate, D-gluconate, besylate, napsylate, tosylate, isethionate, dichloroacetate, benzoate, esylate, gentisate, hippurate, lactobionate, xinafoate, and sebacate salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine were prepared, but all of these failed to crystallize. By contrast, the salts of the present invention are salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine which when prepared were discovered to be both crystalline, and non-hygroscopic. Because of their stability to moisture these salts are useful, inter alia, for preparing dosage forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

One aspect of the present invention pertains to certain salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Compound 1) and pharmaceutically acceptable solvates and hydrates thereof.

One aspect of the present invention pertains to certain salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Compound 1).

5

One aspect of the present invention pertains to salts selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt; and pharmaceutically acceptable solvates and hydrates thereof.

One aspect of the present invention pertains to pharmaceutical compositions comprising a salt of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to processes for preparing a pharmaceutical composition comprising admixing a salt of the present invention, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to bulk pharmaceutical compositions suitable for the manufacture of dosage forms for weight management, comprising a salt of the present invention, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to processes for preparing bulk pharmaceutical compositions suitable for the manufacture of dosage forms for weight management, comprising admixing a salt of the present invention, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to dosage forms comprising a therapeutically effective amount of a salt selected from: a pharmaceutically acceptable salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and pharmaceutically acceptable solvates and hydrates thereof, wherein the dosage form is a non-hygroscopic dosage form.

One aspect of the present invention pertains to dosage forms comprising a therapeutically effective amount of a salt of the present invention.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to the use of salts of the present invention in the manufacture of a medication for weight management in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of treatment of the human or animal body by therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: PXRD of Compound 1 Hemi-edisylate Salt, Form I.

FIG. 2: DSC and TGA of Compound 1 Hemi-edisylate Salt, Form I.

FIG. 3: DMS of Compound 1 Hemi-edisylate Salt, Form I.

FIG. 4: PXRD of Compound 1 Phosphate Salt, Form I.

FIG. 5: DSC and TGA of Compound 1 Phosphate Salt, Form I.

FIG. 6: DMS of Compound 1 Phosphate Salt, Form I.

FIG. 7: PXRD of Compound 1 Citrate Salt Hemihydrate, Form I.

FIG. 8: DSC and TGA of Compound 1 Citrate Salt Hemihydrate, Form I.

FIG. 9: DMS of Compound 1 Citrate Salt Hemihydrate, Form I.

FIG. 10: PXRD of Compound 1 Hemi-oxalate Salt, Form I.

6

FIG. 11: DSC and TGA of Compound 1 Hemi-oxalate Salt, Form I.

FIG. 12: DMS of Compound 1 Hemi-oxalate Salt, Form I.

FIG. 13: PXRD of Compound 1 Succinate Salt, Form I.

FIG. 14: DSC and TGA of Compound 1 Succinate Salt, Form I.

FIG. 15: DMS of Compound 1 Succinate Salt, Form I.

FIG. 16: PXRD of Compound 1 Oxoglutarate Salt, Form I.

FIG. 17: DSC and TGA of Compound 1 Oxoglutarate Salt, Form I.

FIG. 18: DMS of Compound 1 Oxoglutarate Salt, Form I.

FIG. 19: PXRD of Compound 1 Oxoglutarate Salt Solvate, Form I.

FIG. 20: DSC and TGA of Compound 1 Oxoglutarate Salt Solvate, Form I.

FIG. 21: DMS of Compound 1 Oxoglutarate Salt Solvate, Form I.

DETAILED DESCRIPTION

It should be appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term “agonist” refers to a moiety that interacts with and activates a receptor, such as the 5-HT_{2C} serotonin receptor, and initiates a physiological or pharmacological response characteristic of that receptor.

The term “individual” refers to both humans and non-human mammals. Non-human mammals include but are not limited to rodents such as mice and rats, etc. rabbits, dogs, cats, swine, cattle, sheep, horses, and non-human primates such as monkeys and apes, etc.

The term “pharmaceutical composition” refers to a composition comprising at least one active ingredient; including but not limited to Compound 1 and pharmaceutically acceptable salts, solvates and hydrates thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver or by an individual, which includes one or more of the following:

(1) Preventing the disease, for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) Inhibiting the disease, for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease,

condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and

(3) Ameliorating the disease, for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

The term "treatment" as used herein refers to one or more of the following:

(1) prevention of a disease, for example, prevention of a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibition of a disease, for example, inhibition of a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and

(3) amelioration of a disease, for example, amelioration of a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Whether an individual is in need of treatment is a judgment made by a caregiver (e.g. nurse practitioner, physician, physician assistant, nurse, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by Compound 1 and pharmaceutically acceptable salts, solvates and hydrates thereof. Accordingly, Compound 1 and pharmaceutically acceptable salts, solvates and hydrates thereof can be used in a protective or preventive manner; or Compound 1 and pharmaceutically acceptable salts, solvates and hydrates thereof can be used to alleviate, inhibit or ameliorate a disease, condition or disorder.

The term "weight management" as used herein refers to controlling body weight and in the context of the present invention is directed toward weight loss and the maintenance of weight loss (also called weight maintenance herein). In addition to controlling body weight, weight management includes controlling parameters related to body weight, for example, BMI, percent body fat and waist circumference. For example, weight management for an individual who is overweight or obese can mean losing weight with the goal of keeping weight in a healthier range. Also, for example, weight management for an individual who is overweight or obese can include losing body fat or circumference around the waist with or without the loss of body weight.

The term "maintenance of weight loss" or "weight maintenance" as used herein refers to preventing, reducing or controlling weight gain after weight loss. It is well known that weight gain often occurs after weight loss. Weight loss can occur, for example, from dieting, exercising, illness, drug treatment, surgery or any combination of these methods, but often an individual that has lost weight will regain some or all of the lost weight. Therefore, weight maintenance in an individual who has lost weight can include preventing weight gain after weight loss, reducing the amount of weight gained after weight loss, controlling weight gain after weight loss or slowing the rate of weight gain after weight loss.

Salts of the Invention

The present invention is directed, inter alia, to solid, stable, and readily isolable salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and pharmaceutically acceptable solvates and hydrates thereof. The solid state properties of the crystalline forms of salts the present invention are summarized infra.

One aspect of the present invention pertains to salts selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt; and pharmaceutically acceptable solvates and hydrates thereof.

One aspect of the present invention pertains to salts selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt; and pharmaceutically acceptable solvates and hydrates thereof.

One aspect of the present invention pertains to salts selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt hemihydrate; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt; (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt hemihydrate; and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt hemihydrate.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate salt.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt;

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate;

One aspect of the present invention pertains to pharmaceutical compositions comprising a salt of the present invention.

One aspect of the present invention pertains to process for preparing a pharmaceutical composition comprising admixing a salt of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt of the present invention.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for weight management in an individual.

One aspect of the present invention pertains to salts of the present invention, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight loss.

One aspect of the present invention pertains to salts of the present invention, for use in a method of maintenance of weight loss.

One aspect of the present invention pertains to salts of the present invention, for use in a method of decreasing food consumption.

One aspect of the present invention pertains to salts of the present invention, for use in a method of increasing meal-related satiety.

One aspect of the present invention pertains to salts of the present invention, for use in a method of reducing pre-meal hunger.

One aspect of the present invention pertains to salts of the present invention, for use in a method of reducing intra-meal food intake.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management further comprising a reduced-calorie diet.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management further comprising a program of regular exercise.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management further comprising a reduced-calorie diet and a program of regular exercise.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an obese patient with an initial body mass index ≥ 30 kg/m².

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 30 kg/m².

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m².

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management

in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m².

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to salts of the present invention, for use in a method of weight management in combination with phentermine

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention for use in a method of treatment of the human or animal body by therapy.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight loss.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of maintenance of weight loss.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of decreasing food consumption.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of increasing meal-related satiety.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of reducing pre-meal hunger.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of reducing intra-meal food intake.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management further comprising a reduced-calorie diet.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management further comprising a program of regular exercise.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management further comprising a reduced-calorie diet and a program of regular exercise.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an obese patient with an initial body mass index ≥ 30 kg/m².

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 30 kg/m².

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m².

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m².

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the salts and pharmaceutical compositions are for use in a method of weight management in combination with phentermine

Crystalline Salts

Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphs show the same properties in the liquid or gaseous state but they may behave differently in the solid state.

Besides single-component polymorphs, drugs can also exist as salts and other multicomponent crystalline phases. For example, solvates and hydrates may contain an API host and either solvent or water molecules, respectively, as guests. Analogously, when the guest compound is a solid at room temperature, the resulting form is often called a cocrystal. Salts, solvates, hydrates, and cocrystals may show polymorphism as well. Crystalline phases that share the same API host, but differ with respect to their guests, may be referred to as pseudopolymorphs of one another.

Solvates contain molecules of the solvent of crystallization in a definite crystal lattice. Solvates, in which the solvent of crystallization is water, are termed hydrates. Because water is a constituent of the atmosphere, hydrates of drugs may be formed rather easily.

Recently, polymorph screens of 245 compounds revealed that about 90% of them exhibited multiple solid forms. Overall, approximately half the compounds were polymorphic, often having one to three forms. About one-third of the compounds formed hydrates, and about one-third formed solvates. Data from cocrystal screens of 64 compounds showed

that 60% formed cocrystals other than hydrates or solvates. (G. P. Stahly, *Crystal Growth & Design* (2007), 7(6), 1007-1026.)

The present invention is directed, inter alia, to crystalline salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and hydrates and solvates thereof. The crystalline forms of the salts of the present invention can be identified by unique solid state signatures with respect to, for example, differential scanning calorimetry (DSC), X-ray powder diffraction (PXRD), and other solid state methods. Further characterization with respect to water or solvent content of the crystalline salts of the present invention can be gauged by any of the following methods for example, thermogravimetric analysis (TGA), DSC and the like. For DSC, it is known that the temperatures observed will depend upon sample purity, the rate of temperature change, as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by about $\pm 6^\circ$ C. The values reported herein relating to DSC thermograms can also vary by about ± 20 joules per gram. For PXRD, the relative intensities of the peaks can vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can often affect the 2θ values. Therefore, the peak assignments of diffraction patterns can vary by about $\pm 0.2^\circ 2\theta$. The relative intensities of the reported peaks can also vary. For TGA, the features reported herein can vary by about $\pm 5^\circ$ C. The TGA features reported herein can also vary by about $\pm 2\%$ weight change due to, for example, sample variation. Further characterization with respect to hygroscopicity of the crystalline salt can be gauged by, for example, dynamic moisture sorption (DMS). The DMS features reported herein can vary by about $\pm 5\%$ relative humidity. The DMS features reported herein can also vary by about $\pm 5\%$ weight change. The deliquescence relative humidity (DRH) measurements by water activity meter are sensitive to sample quality and quantity. The DRH measurements reported herein can vary by about $\pm 5\%$ RH.

Compound 1 Hemi-Edisylate Salt.

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt, Form I (Compound 1 hemi-edisylate salt, Form I). The physical properties of Compound 1 hemi-edisylate salt, Form I are summarized in Table 1 below.

TABLE 1

Compound 1 Hemi-edisylate Salt, Form I	
PXRD	FIG. 1: Peaks of $\geq 22\%$ relative intensity at 6.00, 11.98, 16.07, 19.70, 20.12, 20.99, 22.39, 22.54, 23.12, 26.77, and $27.44^\circ 2\theta$
TGA	FIG. 2: $< 0.1\%$ weight loss below about 150° C.
DSC	FIG. 2: extrapolated melting onset at $\sim 298^\circ$ C.
DMS	FIG. 3: Non-hygroscopic
DRH	99.7% RH at 25° C.

Form I of Compound 1 hemi-edisylate salt was an anhydrous crystalline material with a melting onset of $\sim 298^\circ$ C. It was non-hygroscopic by DMS analysis, picking up just 0.14% weight out to and including the 95% RH hold at 25° C. The DRH was determined by water activity measurement of saturated aqueous solution with excess solid to be 99.7% RH at 25° C.

Certain X-ray powder diffraction peaks for Form I of Compound 1 hemi-edisylate salt are shown in Table 2 below.

13

TABLE 2

Pos. (°2θ)	Rel. Int. (%)
6.00	76.32
10.31	5.18
11.98	63.17
13.65	15.02
14.63	21.05
16.07	42.02
16.79	9.47
17.98	21.48
19.70	74.89
20.12	53.46
20.64	14.33
20.99	36.94
21.72	3.22
22.39	32.48
22.54	49.14
23.12	100.00
24.13	42.45
24.97	16.43
25.51	7.48
25.88	15.57
26.77	22.17
27.44	42.76
27.91	6.99
28.78	6.82
29.44	10.45
29.70	6.33
30.18	18.52
30.85	2.77
31.29	3.71
32.65	3.88
33.12	5.93
33.74	3.51
34.32	6.72
35.06	5.31
35.46	6.63
35.86	11.13
36.23	7.83
37.63	2.62
38.95	5.33
39.27	4.59

One aspect of the present invention is directed to a Compound 1 hemi-edisylate salt having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 23.12°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 6.00°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 23.12° and about 6.00°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 23.12° and about 19.70°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 23.12°, about 6.00°, and about 19.70°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 23.12°, about 6.00°, about 19.70°, about 11.98°, about 20.12°, about 22.54°, and about 27.44°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 23.12°, about 6.00°, about 19.70°, about 11.98°, about 20.12°, about 22.54°, about 27.44°, about 16.07°, about 20.99°, and about 22.39°. One aspect of the present invention is directed to a Compound 1 hemi-edisylate salt having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 2. In some embodiments, the salt has an X-ray powder diffraction pattern substantially as shown in FIG. 1, wherein by “substantially” is meant that the reported peaks can vary by about $\pm 0.2^\circ 2\theta$ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the Compound 1 hemi-edisylate salt has a differential scanning calorimetry thermogram com-

14

prising an endotherm with an extrapolated onset temperature between about 285° C. and about 315° C. In some embodiments, the Compound 1 hemi-edisylate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 298° C. In some embodiments, the Compound 1 hemi-edisylate salt has a differential scanning calorimetry thermogram comprising an endotherm with an associated heat flow of about 101 joules per gram. In some embodiments, the Compound 1 hemi-edisylate salt has a thermogravimetric analysis profile substantially as shown in FIG. 2, wherein by “substantially” is meant that the reported TGA features can vary by about $\pm 5^\circ$ C. and by about $\pm 2\%$ weight change.

In some embodiments, the Compound 1 hemi-edisylate salt has a differential scanning calorimetry thermogram substantially as shown in FIG. 2, wherein by “substantially” is meant that the reported DSC features can vary by about $\pm 6^\circ$ C. and by about ± 20 joules per gram.

In some embodiments, the Compound 1 hemi-edisylate salt has a dynamic moisture sorption profile substantially as shown in FIG. 3, wherein by “substantially” is meant that the reported DMS features can vary by about $\pm 5\%$ relative humidity and by about $\pm 5\%$ weight change.

Form I of Compound 1 hemi-edisylate salt can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 hemi-edisylate salt can be prepared as described in Example 4. In some embodiments, Form I of Compound 1 hemi-edisylate salt can be prepared by slurrying crystalline Compound 1 hemi-edisylate salt containing one or more crystalline forms other than Form I. In some embodiments, Form I of Compound 1 hemi-edisylate salt can be prepared by recrystallizing crystalline Compound 1 hemi-edisylate salt containing one or more crystalline forms other than Form I. Compound 1 Phosphate Salt

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate, Form I (Compound 1 phosphate salt, Form I). The physical properties of Form I of Compound 1 phosphate salt are summarized in Table 3 below.

TABLE 3

Compound 1 Phosphate salt, Form I	
PXRD	FIG. 4: Peaks of $\geq 15\%$ relative intensity at 7.45, 14.87, 16.51, 18.16, 19.27, 20.19, 21.05, 23.19, 25.06, 25.77, 28.61, and 29.96 °2θ
TGA	FIG. 5: <0.03% weight loss up to about 178° C.
DSC	FIG. 5: extrapolated onset temperature about 208° C.; enthalpy of fusion about 113 J/g
DMS	FIG. 6: about 0.14% weight gain at 90% RH
DRH	100% RH at 25° C.

The title salt was a 1:1 salt based on stoichiometry determination. The melting onset by DSC was $\sim 208^\circ$ C. The TGA result for a crystalline sample prior to the n-propanol slurry is consistent with an anhydrous salt. It was non-hygroscopic, picking up 0.14% weight out to and including the 90% RH hold at 25° C. during DMS analysis. The title salt was non-deliquescent; the DRH by water activity measurement of a saturated solution in water with excess solid was 100% RH at 25° C.

Certain X-ray powder diffraction peaks for Form I of Compound 1 phosphate salt are shown in Table 4 below.

15

TABLE 4

Pos. (°2 θ)	Rel. Int. (%)
7.45	30.59
10.57	1.00
12.37	0.89
14.87	54.02
16.51	16.28
18.16	33.52
18.48	4.45
19.27	100.00
20.19	41.74
21.05	20.88
22.29	8.70
22.78	2.99
23.19	24.55
23.75	4.80
24.42	10.14
24.78	11.41
25.06	74.60
25.77	54.32
26.79	1.40
27.25	5.21
28.61	15.30
28.96	11.18
29.96	15.85
30.15	10.60
30.61	5.36
31.09	2.76
31.47	4.27
31.68	4.57
32.22	6.36
32.91	11.02
33.36	4.31
33.65	3.13
34.31	5.55
34.80	1.85
35.34	5.80
36.18	5.37
36.62	7.62
37.64	2.73
38.25	2.15
38.48	3.15
38.99	3.49
39.80	2.28

One aspect of the present invention is directed to a Compound 1 phosphate salt having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 19.27°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 25.06°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 19.27° and about 25.06°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 19.27° and about 25.77°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 19.27°, about 25.06°, and about 25.77°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 19.27°, about 25.06°, about 25.77°, about 14.87°, about 20.19°, about 18.16°, and about 7.45°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 19.27°, about 25.06°, about 25.77°, about 14.87°, about 20.19°, about 18.16°, and about 7.45°. One aspect of the present invention is directed to a Compound 1 phosphate salt having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 4. In some embodiments, the salt has an X-ray powder diffraction pattern substantially as shown in FIG. 4, wherein by “substantially” is meant that the reported peaks can vary by about $\pm 0.2^\circ 2\theta$ and also that the relative intensities of the reported peaks can vary.

16

In some embodiments, the Compound 1 phosphate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 190° C. and about 220° C. In some embodiments, the Compound 1 phosphate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 208° C. In some embodiments, the Compound 1 phosphate salt has a differential scanning calorimetry thermogram comprising an endotherm with an associated heat flow of about 113 joules per gram. In some embodiments, the Compound 1 phosphate salt has a thermogravimetric analysis profile substantially as shown in FIG. 5, wherein by “substantially” is meant that the reported TGA features can vary by about $\pm 5^\circ$ C. and by about $\pm 2\%$ weight change.

In some embodiments, the Compound 1 phosphate salt has a differential scanning calorimetry thermogram substantially as shown in FIG. 5, wherein by “substantially” is meant that the reported DSC features can vary by about $\pm 6^\circ$ C. and by about ± 20 joules per gram.

In some embodiments, the Compound 1 phosphate salt has a dynamic moisture sorption profile substantially as shown in FIG. 6, wherein by “substantially” is meant that the reported DMS features can vary by about $\pm 5\%$ relative humidity and by about $\pm 5\%$ weight change.

Form I of Compound 1 phosphate salt can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 phosphate salt can be prepared as described in Example 9. In some embodiments, Form I of Compound 1 phosphate salt can be prepared by slurring crystalline Compound 1 phosphate salt containing one or more crystalline forms other than Form I. In some embodiments, Form I of Compound 1 phosphate salt can be prepared by recrystallizing crystalline Compound 1 phosphate salt containing one or more crystalline forms other than Form I.

Compound 1 Citrate Salt Hemihydrate

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt hemihydrate, Form I (Compound 1 citrate salt hemihydrate, Form I). The physical properties of Compound 1 citrate salt hemihydrate, Form I are summarized in Table 5 below.

TABLE 5

Compound 1 Citrate Salt Hemihydrate, Form I	
PXRD	FIG. 7: Peaks of $\geq 10\%$ relative intensity at 11.93, 13.01, 17.12, 18.64, 19.11, 19.69, 20.73, 21.74, 24.05, 24.52, 24.81, 26.12, and 26.92 $^\circ 2\theta$
TGA	FIG. 8: 2.6% weight loss up to about 110° C.
DSC	FIG. 8: onset of dehydration about 80° C.
DMS	FIG. 9: 0.50% weight gain up to 90% RH
DRH	100% RH at 25° C.

TGA data for Form I of Compound 1 citrate salt hemihydrate, showed that it was solvated. The mass loss matches closely with a hemihydrate (observed 2.6%, theoretical 2.3%). The onset of dehydration is near 80° C. for the scan rate, 10° C./min.

Form I of Compound 1 citrate salt hemihydrate lost only a small amount of its water of hydration during the drying step at 40° C. and $\sim 1\%$ RH for 1 h. It was not hygroscopic, picking up just 0.50% out to and including the 90% RH hold at 25° C., and not deliquescent. The DRH was determined by water activity measurement of saturated aqueous solution with excess solid to be 100% RH at 25° C.

17

Certain X-ray powder diffraction peaks for Form I of Compound 1 citrate salt hemihydrate are shown in Table 6 below.

TABLE 6

Pos. (°2θ)	Rel. Int. (%)
5.21	0.59
7.97	2.63
10.42	0.78
11.93	100.00
13.01	21.60
13.39	2.56
14.59	0.68
15.05	3.43
15.82	9.09
17.12	14.71
18.11	6.66
18.25	9.72
18.64	48.80
19.11	11.23
19.69	10.74
20.73	10.25
20.90	6.24
21.21	4.73
21.74	10.41
22.05	4.67
22.61	0.89
23.14	9.91
24.05	22.56
24.52	26.69
24.81	22.12
25.39	6.32
26.12	22.84
26.92	15.24
27.45	2.48
27.69	4.21
28.45	2.64
29.62	5.72
30.45	6.04
30.86	1.49
31.21	3.45
31.53	2.29
31.86	6.20
32.39	4.50
32.48	4.06
33.12	4.05
33.46	1.21
33.80	2.09
34.56	1.04
35.17	0.49
35.86	1.23
36.20	1.62
36.50	2.29
36.78	4.52
37.31	1.65
37.80	4.73
38.26	1.86
39.08	2.14
39.60	0.99

One aspect of the present invention is directed to a Compound 1 citrate salt hemihydrate having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 11.93° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 18.64° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 11.93° and about 18.64° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 11.93° and about 24.52° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 11.93° , about 18.64° , and about 24.52° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 11.93° , about 18.64° , about 24.52° , about 26.12° , about 24.05° , about 24.81° , and about 13.01° .

18

In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 11.93° , about 18.64° , about 24.52° , about 26.12° , about 24.05° , about 24.81° , about 13.01° , about 26.92° , about 17.12° , and about 19.11° . One aspect of the present invention is directed to a Compound 1 citrate salt hemihydrate having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 6. In some embodiments, the salt has an X-ray powder diffraction pattern substantially as shown in FIG. 7, wherein by “substantially” is meant that the reported peaks can vary by about $\pm 0.2^\circ 2\theta$ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the Compound 1 citrate salt hemihydrate has a thermogravimetric analysis profile substantially as shown in FIG. 8, wherein by “substantially” is meant that the reported TGA features can vary by about $\pm 5^\circ \text{C}$. and by about $\pm 2\%$ weight change.

In some embodiments, the Compound 1 citrate salt hemihydrate has a differential scanning calorimetry thermogram substantially as shown in FIG. 8, wherein by “substantially” is meant that the reported DSC features can vary by about $\pm 6^\circ \text{C}$. and by about ± 20 joules per gram.

In some embodiments, the Compound 1 citrate salt hemihydrate has a dynamic moisture sorption profile substantially as shown in FIG. 9, wherein by “substantially” is meant that the reported DMS features can vary by about $\pm 5\%$ relative humidity and by about $\pm 5\%$ weight change.

Form I of Compound 1 citrate salt hemihydrate can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 citrate salt hemihydrate can be prepared as described in Example 3. In some embodiments, Form I of Compound 1 citrate salt hemihydrate can be prepared by slurrying crystalline Compound 1 citrate salt hemihydrate containing one or more crystalline forms other than Form I. In some embodiments, Form I of Compound 1 citrate salt hemihydrate can be prepared by recrystallizing crystalline Compound 1 citrate salt hemihydrate containing one or more crystalline forms other than Form I.

Compound 1 Hemi-Oxalate Salt

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-oxalate, Form I (Compound 1 hemi-oxalate salt, Form I). The physical properties of Compound 1 hemi-oxalate salt, Form I are summarized in Table 7 below.

TABLE 7

Compound 1 Hemi-oxalate Salt, Form I	
PXRD	FIG. 10: Peaks of $\geq 10\%$ relative intensity at 6.34, 14.25, 14.51, 16.49, 21.69, 22.03, 24.06, 24.51, 24.92, 25.37, 31.85, 33.49, and $33.91^\circ 2\theta$
TGA	FIG. 11: $< 0.3\%$ weight loss up to about 150°C .
DSC	FIG. 11: extrapolated onset temperature about 212°C .
DMS	FIG. 12: non-hygroscopic and non-deliquescent at 25°C .
DRH	100% RH at 25°C .

Form I of Compound 1 hemi-oxalate salt was anhydrous and displayed a melting onset temperature about 212°C . with weight loss by TGA starting just prior to the melting onset. It was determined to be non-hygroscopic and non-deliquescent at 25°C . The DRH was determined by water activity measurement of saturated aqueous solution with excess solid to be 100% RH at 25°C .

Certain X-ray powder diffraction peaks for Form I of Compound 1 hemi-oxalate salt are shown in Table 8 below.

19

TABLE 8

Pos. (°2θ)	Rel. Int. (%)
6.34	100.00
10.81	0.92
11.45	1.22
12.65	5.04
14.25	23.10
14.51	18.93
15.43	3.19
16.49	10.86
17.14	2.19
18.31	2.20
18.98	4.57
19.82	7.58
21.03	2.13
21.69	51.81
22.03	27.18
22.56	3.78
23.03	1.90
24.06	22.77
24.51	13.01
24.92	13.18
25.37	44.12
26.60	8.81
27.13	6.17
27.45	4.50
27.81	5.49
28.38	4.45
29.12	3.46
30.44	3.29
30.84	3.95
31.85	48.33
32.76	1.74
33.49	15.33
33.91	12.30
34.53	5.38
35.71	1.00
36.50	1.20
37.60	2.62
38.37	1.52
39.39	1.31

One aspect of the present invention is directed to a Compound 1 hemi-oxalate salt having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 6.34°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 21.69°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.34° and about 21.69°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.34° and about 31.85°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.34°, about 21.69°, and about 31.85°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.34°, about 21.69°, about 31.85°, about 25.37°, about 22.03°, about 14.25°, and about 24.06°. In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.34°, about 21.69°, about 31.85°, about 25.37°, about 22.03°, about 14.25°, about 24.06°, about 14.51°, about 33.49°, and about 24.92°. One aspect of the present invention is directed to a Compound 1 hemi-oxalate salt having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 8. In some embodiments, the salt has an X-ray powder diffraction pattern substantially as shown in FIG. 10, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2 °2θ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the Compound 1 hemi-oxalate salt has a differential scanning calorimetry thermogram compris-

20

ing an endotherm with an extrapolated onset temperature between about 195° C. and about 225° C. In some embodiments, the Compound 1 hemi-oxalate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 212° C. In some embodiments, the Compound 1 hemi-oxalate salt has a thermogravimetric analysis profile substantially as shown in FIG. 11, wherein by “substantially” is meant that the reported TGA features can vary by about ±5° C. and by about ±2% weight change.

In some embodiments, the Compound 1 hemi-oxalate salt has a differential scanning calorimetry thermogram substantially as shown in FIG. 11, wherein by “substantially” is meant that the reported DSC features can vary by about ±6° C. and by about ±20 joules per gram.

In some embodiments, the Compound 1 hemi-oxalate salt has a dynamic moisture sorption profile substantially as shown in FIG. 12, wherein by “substantially” is meant that the reported DMS features can vary by about ±5% relative humidity and by about ±5% weight change.

Form I of Compound 1 hemi-oxalate salt can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 hemi-oxalate salt can be prepared as described in Example 4. In some embodiments, Form I of Compound 1 hemi-oxalate salt can be prepared by slurrying crystalline Compound 1 hemi-oxalate salt containing one or more crystalline forms other than Form I. In some embodiments, Form I of Compound 1 hemi-oxalate salt can be prepared by recrystallizing crystalline Compound 1 hemi-oxalate salt containing one or more crystalline forms other than Form I.

Compound 1 Succinate Salt

One aspect of the present invention pertains to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate, Form I (Compound 1 succinate salt, Form I). The physical properties of Compound 1 succinate salt, Form I are summarized in Table 9 below.

TABLE 9

Compound 1 Succinate Salt, Form I	
PXRD	FIG. 13: Peaks of ≥5% relative intensity at 12.53, 13.63, 15.64, 17.64, 20.65, 21.20, 24.35, 25.11, 26.54, 27.14, and 27.62 °2θ
TGA	FIG. 14: <0.4% weight loss up to about 125° C.
DSC	FIG. 14: extrapolated onset temperature about 179° C.; enthalpy of fusion 141 J/g
DMS	FIG. 15: 0.07% weight gain at 90% RH
DRH	100% RH at 25° C.

Compound 1 succinate salt, Form I showed a melting onset by DSC of 179.1° C. TGA showed no residual solvent, but did show apparent loss of significant succinic acid prior to the melting onset. It was non-hygroscopic by DMS analysis, picking up 0.07% weight out to and including the 90% RH hold at 25° C. The DRH was determined by water activity measurement of saturated aqueous solution with excess solid to be 100% RH at 25° C.

Certain X-ray powder diffraction peaks for Form I of Compound 1 succinate salt are shown in Table 10 below.

TABLE 10

Pos. (°2θ)	Rel. Int. (%)
6.84	1.00
11.58	2.35
12.53	6.13

TABLE 10-continued

Pos. ($^{\circ}2\theta$)	Rel. Int. (%)
12.71	3.50
13.63	7.75
15.07	1.31
15.64	34.98
16.10	3.90
16.41	2.86
17.64	13.76
19.59	0.24
20.34	4.78
20.65	38.05
21.20	5.87
21.61	1.36
22.18	1.17
23.21	2.29
24.35	14.11
25.11	24.83
25.51	4.64
26.05	3.56
26.54	14.35
27.14	7.58
27.62	100.00
28.44	2.23
30.40	1.02
31.73	4.21
32.34	0.51
32.88	0.89
33.60	0.24
34.36	0.95
35.67	1.66
36.34	0.96
36.91	2.16
37.08	1.53
38.00	1.19
38.61	2.36
38.97	0.70
39.59	1.01

One aspect of the present invention is directed to a Compound 1 succinate salt having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 27.62° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at about 20.65° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 27.62° and about 20.65° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 27.62° and about 15.64° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 27.62° , about 20.65° , about 15.64° , about 25.11° , about 26.54° , about 24.35° , and about 17.64° . In some embodiments, the salt has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at about 27.62° , about 20.65° , about 15.64° , about 25.11° , about 26.54° , about 24.35° , about 17.64° , about 13.63° , about 27.14° , and about 12.53° . One aspect of the present invention is directed to a Compound 1 succinate salt having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 10. In some embodiments, the salt has an X-ray powder diffraction pattern substantially as shown in FIG. 13, wherein by “substantially” is meant that the reported peaks can vary by about $\pm 0.2^{\circ}2\theta$ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the Compound 1 succinate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 160°C. and about 190°C. In some embodiments, the Compound 1 succinate salt has a differential scan-

ning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 179°C. In some embodiments, the Compound 1 succinate salt has a differential scanning calorimetry thermogram comprising an endotherm with an associated heat flow of about 141 joules per gram. In some embodiments, the Compound 1 succinate salt has a thermogravimetric analysis profile substantially as shown in FIG. 14, wherein by “substantially” is meant that the reported TGA features can vary by about $\pm 5^{\circ}\text{C.}$ and by about $\pm 2\%$ weight change.

In some embodiments, the Compound 1 succinate salt has a differential scanning calorimetry thermogram substantially as shown in FIG. 14, wherein by “substantially” is meant that the reported DSC features can vary by about $\pm 6^{\circ}\text{C.}$ and by about ± 20 joules per gram.

In some embodiments, the Compound 1 succinate salt has a dynamic moisture sorption profile substantially as shown in FIG. 15, wherein by “substantially” is meant that the reported DMS features can vary by about $\pm 5\%$ relative humidity and by about $\pm 5\%$ weight change.

Form I of Compound 1 succinate salt can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 succinate salt can be prepared as described in Example 5. In some embodiments, Form I of Compound 1 succinate salt can be prepared by slurrying crystalline Compound 1 succinate salt containing one or more crystalline forms other than Form I. In some embodiments, Form I of Compound 1 succinate salt can be prepared by recrystallizing crystalline Compound 1 succinate salt containing one or more crystalline forms other than Form I.

Compound 1 Oxoglutarate Salt

One aspect of the present invention pertains to a crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt (Compound 1 oxoglutarate salt). In some embodiments, the crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt is Form I (Compound 1 oxoglutarate salt, Form I). The physical properties of Form I of Compound 1 oxoglutarate salt are summarized in Table 11 below.

TABLE 11

Compound 1 Oxoglutarate Salt, Form I	
PXRD	FIG. 16: Peaks of $\geq 15\%$ relative intensity at 7.86 , 13.39 , 18.71 , 19.10 , 20.06 , 21.22 , 22.84 , 23.18 , 23.57 , 24.67 , 25.37 , and $26.81^{\circ}2\theta$
TGA	FIG. 17: negligible weight loss below about 120°C.
DSC	FIG. 17: extrapolated onset temperature about 115°C. ; enthalpy of fusion 114 J/g
DMS	FIG. 18: $\sim 0.106\%$ weight gain at about 90% RH

The title salt was anhydrous material by TGA with a melting onset of $\sim 115^{\circ}\text{C.}$ by DSC. It was non-hygroscopic by DMS. Compound 1 oxoglutarate salt was non-hygroscopic by DMS analysis, picking up about 0.106% out to and including the 90% RH hold at 25°C.

Certain X-ray powder diffraction peaks for Form I of Compound 1 oxoglutarate salt are shown in Table 12 below.

TABLE 12

Pos. ($^{\circ}2\theta$)	Rel. Int. (%)
7.86	41.21
10.09	6.35
10.65	3.29
11.45	4.60

TABLE 12-continued

Pos. (°2θ)	Rel. Int. (%)
13.39	100.00
14.30	14.50
15.12	1.59
15.69	3.23
17.40	2.12
18.71	31.16
19.10	46.89
19.37	5.60
20.06	38.48
21.22	55.23
21.93	3.04
22.46	8.90
22.84	15.51
23.18	48.32
23.57	58.00
23.82	10.53
24.29	9.84
24.67	48.09
25.12	9.56
25.37	16.94
25.75	12.57
26.81	32.66
27.39	2.32
27.83	3.40
28.41	5.39
29.43	5.16
29.62	5.28
30.62	3.15
31.63	2.70
32.16	2.09
32.76	5.80
33.64	4.97
34.30	3.31
34.66	6.12
35.50	2.04
35.87	3.24
36.20	2.67
36.71	1.15
37.53	2.34
38.13	2.72
38.54	4.38
38.86	4.03

One aspect of the present invention is directed to a crystalline form of Compound 1 oxoglutarate salt having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 13.39°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 23.57°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.39° and about 23.57°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.39°, about 23.57°, and about 21.22°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.39°, about 23.57°, about 21.22°, about 23.18°, about 24.67°, about 19.10°, and about 7.86°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.39°, about 23.57°, about 21.22°, about 23.18°, about 24.67°, about 19.10°, about 7.86°, about 20.06°, about 18.71°, and about 25.37°. One aspect of the present invention is directed to a crystalline form of Compound 1 oxoglutarate salt having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 12. In some embodiments, the crystalline form has an X-ray powder diffraction pattern substantially as shown in FIG. 16, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2 °2θ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 100° C. and about 130° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 115° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a differential scanning calorimetry thermogram comprising an endotherm with an associated heat flow of about 114 joules per gram. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a thermogravimetric analysis profile substantially as shown in FIG. 17, wherein by “substantially” is meant that the reported TGA features can vary by about ±5° C. and by about ±2% weight change.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a differential scanning calorimetry thermogram substantially as shown in FIG. 17, wherein by “substantially” is meant that the reported DSC features can vary by about ±6° C. and by about ±20 joules per gram.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt has a dynamic moisture sorption profile substantially as shown in FIG. 18, wherein by “substantially” is meant that the reported DMS features can vary by about ±5% relative humidity and by about ±5% weight change.

Form I of Compound 1 oxoglutarate salt can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 oxoglutarate salt can be prepared as described in Example 6. In some embodiments, Form I of Compound 1 oxoglutarate salt can be prepared by slurrying crystalline Compound 1 oxoglutarate salt containing one or more crystalline forms other than Form I. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt can be prepared by recrystallizing crystalline Compound 1 oxoglutarate salt containing one or more crystalline forms other than Form I.

Compound 1 Oxoglutarate Salt Solvate

One aspect of the present invention pertains to a crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate (Compound 1 oxoglutarate salt solvate). In some embodiments, the crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate is Form I (Compound 1 oxoglutarate salt solvate, Form I). The physical properties of Form I of Compound 1 oxoglutarate salt solvate are summarized in Table 13 below.

TABLE 13

Compound 1 Oxoglutarate Salt Solvate, Form I	
PXRD	FIG. 19: Peaks of ≥30% relative intensity at 6.29, 11.53, 12.51, 12.97, 14.76, 18.72, 22.65, 23.34, 23.71, 24.83, 25.16, and 26.02 °2θ
TGA	FIG. 20: about 5.2% weight loss up to about 115° C.
DSC	FIG. 20: desolvation extrapolated onset temperature about 91° C.; second endotherm extrapolated onset temperature about 113° C.
DMS	FIG. 21: ~1.518% weight gain at about 90% RH

The title salt was a solvated crystalline material with a desolvation onset of ~91° C. followed closely by another endotherm at ~113° C.; both determined by DSC. Compound 1 oxoglutarate salt solvate, had a weight loss of ~5.2% (desolvation onset ~84° C. by TGA) out to ~110° C. This weight loss was slightly higher than the theoretical value (5.0%) for

a monohydrate and slight lower than the theoretical value (5.7%) for a solvate. The desolvation is followed by degradation.

The title salt was non-hygroscopic by DMS analysis, losing about 1.518% out to and including the 90% RH hold at 25° C. This type of hysteresis is typically associated with displacement of an organic solvent by water and often results in a form change. However, by PXRD analysis, the crystal form appeared unchanged

Certain X-ray powder diffraction peaks for Form I of Compound 1 oxoglutarate salt solvate are shown in Table 14 below.

TABLE 14

Pos. (°2θ)	Rel. Int. (%)
6.29	43.52
7.88	6.60
11.53	84.11
11.88	24.85
12.51	59.10
12.97	44.83
13.30	20.61
14.22	15.76
14.76	37.04
14.87	28.42
15.88	3.79
17.41	3.32
18.47	21.06
18.72	33.99
19.08	9.33
20.03	8.32
20.70	17.34
21.21	12.16
21.50	17.72
22.25	15.99
22.65	62.16
23.34	38.86
23.71	32.16
24.83	35.84
25.16	38.94
26.02	100.00
26.47	14.65
27.089	25.48
27.69	7.40
28.33	9.36
28.88	8.66
29.54	14.13
29.82	9.78
30.66	3.22
31.30	2.74
31.94	6.36
33.01	8.23
34.03	2.72
34.43	5.46
36.75	3.46
37.35	3.43

One aspect of the present invention is directed to a crystalline form of Compound 1 oxoglutarate salt solvate having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 26.02°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising a peak, in terms of 2θ, at about 11.53°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 26.02° and about 11.53°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 26.02° and about 22.65°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 26.02°, about 11.53°, and about 22.65°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 26.02°, about 11.53°,

about 22.65°, about 12.51°, about 12.97°, about 6.29°, and about 25.16°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 26.02°, about 11.53°, about 22.65°, about 12.51°, about 12.97°, about 6.29°, about 25.16°, about 23.34°, about 14.76°, and about 24.83°. One aspect of the present invention is directed to a crystalline form of Compound 1 oxoglutarate salt solvate having an X-ray powder diffraction pattern comprising one or more peaks listed in Table 14. In some embodiments, the crystalline form has an X-ray powder diffraction pattern substantially as shown in FIG. 19, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2 °2θ and also that the relative intensities of the reported peaks can vary.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 75° C. and about 105° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 91° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 100° C. and about 130° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 75° C. and about 105° C., and an endotherm with an extrapolated onset temperature between about 100° C. and about 130° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature at about 91° C., and an endotherm with an extrapolated onset temperature at about 113° C. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a thermogravimetric analysis profile substantially as shown in FIG. 20, wherein by “substantially” is meant that the reported TGA features can vary by about ±5° C. and by about ±2% weight change.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a differential scanning calorimetry thermogram substantially as shown in FIG. 20, wherein by “substantially” is meant that the reported DSC features can vary by about ±6° C. and by about ±20 joules per gram.

In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate has a dynamic moisture sorption profile substantially as shown in FIG. 21, wherein by “substantially” is meant that the reported DMS features can vary by about ±5% relative humidity and by about ±5% weight change.

Form I of Compound 1 oxoglutarate salt solvate can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments Form I of Compound 1 oxoglutarate salt solvate can be prepared as described in Example 7. In some embodiments, Form I of Compound 1 oxoglutarate salt solvate can be prepared by slurrying crystalline Compound 1 oxoglutarate salt solvate containing one or more crystalline forms other than Form I. In some embodiments, the crystalline form of Compound 1 oxoglutarate salt solvate can be prepared by recrystallization.

tallizing crystalline Compound 1 oxoglutarate salt solvate containing one or more crystalline forms other than Form I.

One aspect of the present invention pertains to processes for preparing a pharmaceutical composition comprising admixing a crystalline salt of the present invention, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to processes for preparing a bulk pharmaceutical composition comprising admixing a crystalline salt of the present invention, and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a crystalline salt of the present invention.

One aspect of the present invention pertains to the use of crystalline salts of the present invention, in the manufacture of a medicament for weight management in an individual.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight loss.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of maintenance of weight loss.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of decreasing food consumption.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of increasing meal-related satiety.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of reducing pre-meal hunger.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of reducing intra-meal food intake.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management further comprising a reduced-calorie diet.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management further comprising a program of regular exercise.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management further comprising a reduced-calorie diet and a program of regular exercise.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an obese patient with an initial body mass index $\geq 30 \text{ kg/m}^2$.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight

related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 30 \text{ kg/m}^2$.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 27 \text{ kg/m}^2$.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 25 \text{ kg/m}^2$.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in an individual with an initial body mass index $\geq 25 \text{ kg/m}^2$ in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to crystalline salts of the present invention, for use in a method of weight management in combination with phentermine.

Hydrates and Solvates

It is understood that when the phrase "pharmaceutically acceptable salts, solvates, and hydrates" or the phrase "pharmaceutically acceptable salt, solvate, or hydrate" is used when referring to compounds described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of the compounds, pharmaceutically acceptable salts of the compounds, as well as pharmaceutically acceptable solvates and/or hydrates of pharmaceutically acceptable salts of the compounds. It is also understood that when the phrase "pharmaceutically acceptable solvates and hydrates" or the phrase "pharmaceutically acceptable solvate or hydrate" is used when referring to compounds described herein that are salts, it embraces pharmaceutically acceptable solvates and/or hydrates of such salts.

It will be apparent to those skilled in the art that the dosage forms described herein may comprise, as the active component, either a salts or crystalline form thereof as described herein, or a solvate or hydrate thereof. Moreover, various hydrates and solvates of the salts or crystalline form thereof described herein will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of K. J. Guillory, "Gen-

eration of Polymorphs, Hydrates, Solvates, and Amorphous Solids,” in: *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999.

Accordingly, one aspect of the present invention pertains to methods of administering hydrates and solvates of salts or crystalline forms thereof described herein and/or their pharmaceutically acceptable salts, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, Del.), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, Conn.).

Isotopes

The present disclosure includes all isotopes of atoms occurring in the present salts and crystalline forms thereof. Isotopes include those atoms having the same atomic number but different mass numbers. One aspect of the present invention includes every combination of one or more atoms in the present salts and crystalline forms thereof that is replaced with an atom having the same atomic number but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^1H or ^{12}C , found in one the present salts and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as ^2H or ^3H (replacing ^1H), or ^{13}C , ^{13}C , or ^{14}C (replacing ^{12}C). A salt wherein such a replacement has taken place is commonly referred to as being isotopically-labeled. Isotopic-labeling of the present salts and crystalline forms thereof can be accomplished using any one of a variety of different synthetic methods known to those of ordinary skill in the art and they are readily credited with understanding the synthetic methods and available reagents needed to conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^2H (deuterium) and ^3H (tritium). Isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C . Isotopes of nitrogen include ^{13}N and ^{15}N . Isotopes of oxygen include ^{15}O , ^{17}O , and ^{18}O . An isotope of fluorine includes ^{18}F . An isotope of sulfur includes ^{35}S . An isotope of chlorine includes ^{36}Cl . Isotopes of bromine include ^{75}Br , ^{76}Br , ^{77}Br , and ^{82}Br . Isotopes of iodine include ^{123}I , ^{124}I , ^{125}I , and ^{131}I . Another aspect of the present invention includes compositions, such as, those prepared during synthesis, pre-formulation, and the like, and pharmaceutical compositions, such as, those prepared with the intent of using in a mammal for the treatment of one or more of the disorders described herein, comprising one or more of the present salts and crystalline forms thereof, wherein the naturally occurring distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and pharmaceutical compositions comprising salts and crystalline forms thereof as described herein wherein the salt is enriched at one or more positions with an isotope other than the most naturally abundant isotope. Methods are readily available to measure such isotope perturbations or enrichments, such as, mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as, radio-detectors used in connection with HPLC or GC.

Pharmaceutical Compositions

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more salts according to any of the salt embodiments disclosed herein and

one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a salt according to any of the salt embodiments disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments pertain to pharmaceutical compositions comprising any subcombination of salts according to any of the salt embodiments disclosed herein.

Another aspect of the present invention pertains to methods of producing pharmaceutical compositions comprising admixing one or more salts according to any of the salt embodiments disclosed herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to a method of producing a pharmaceutical composition comprising admixing a salt according to any of the salt embodiments disclosed herein and a pharmaceutically acceptable carrier. Some embodiments pertain to a methods of producing pharmaceutical compositions comprising admixing any subcombination of salts according to any of the salt embodiments disclosed herein and a pharmaceutically acceptable carrier.

Salts of the present invention or a solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 5-HT_{2C}-receptor modulators. The term “active ingredient” as defined in the context of a “pharmaceutical composition” and is intended to mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an “inactive ingredient” which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the salts of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the salt employed or on whether an acute or chronic disease state is treated or prophylaxis conducted or on whether further active compounds are administered in addition to the salts of the present invention. Representative doses of the present invention include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate from the patient’s physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular salt employed, whether a drug delivery system is utilized, on

whether an acute or chronic disease state is being treated or prophylaxis conducted or on whether further active compounds are administered in addition to the salts of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the salts and/or compositions of this invention is selected in accordance with a variety of factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one salt according to any of the salt embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when the salts of the present invention are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as 5-HT_{2C}-receptor modulators, for the treatment of a 5-HT_{2C}-receptor-associated disease or disorders in companion animals (e.g., cats, dogs, etc.) and in livestock animals (e.g., cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such salts in such settings.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a pharmaceutical composition of the present invention.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight loss.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of maintenance of weight loss.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of decreasing food consumption.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of increasing meal-related satiety.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of reducing pre-meal hunger.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of reducing intra-meal food intake.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management further comprising a reduced-calorie diet.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management further comprising a program of regular exercise.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management further comprising a reduced-calorie diet and a program of regular exercise.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an obese patient with an initial body mass index ≥ 30 kg/m².

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 30 kg/m².

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m².

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m².

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in an individual with an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related co-morbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to pharmaceutical compositions of the present invention, for use in a method of weight management in combination with phentermine.

Hygroscopicity

Many compounds and salts are sensitive to the presence of water vapor or moisture. When compounds and salts interact with moisture, they retain water by either bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, formation of a solution (deliquescence). Deliquescence occurs when a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, the liquid film surrounding the solid is saturated. This process is dictated by vapor diffusion and heat transport rates. (Gibson, *Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*, Informa Health Care, 2001; Kontny et al., *Pharmaceutical Research*, 1987, 4(2), 104-12.)

The opposite of deliquescence is efflorescence, which occurs when a crystal loses water of crystallization below a critical vapor pressure. For example Griesser and Burger (*International Journal of Pharmaceutics*, 1995, 120(1), 83-93) found that caffeine hydrate lost its water of crystallization even at 61% RH. It has also been observed that the three known polymorphs of oxytetracycline have different hygroscopicity profiles. (Burger et al., *Acta Pharmaceutica Technologica*, 1985, 31(4), 230-5.)

Moisture is also an important factor that can affect the stability of candidate drugs and their formulations. Sorption of water molecules onto a candidate drug (or excipient) can often induce hydrolysis (see, e.g., Yoshioka and Carstensen, *Journal of Pharmaceutical Sciences*, 1990, 79(9), 799-801). Other properties such as crystal structure, powder flow, compaction, lubricity, dissolution rate and polymer film permeability may also be effected by moisture adsorption (Ahlneck and Zografi, *International Journal of Pharmaceutics*, 1990, 62(2-3), 87-95.)

The influence that moisture has on stability depends on how strongly it is bound, i.e., it depends on whether the moisture is in a free or a bound state. Generally, degradation arises as a function of free water, which may be due to its ability to change the pH of the surfaces of drug and excipient. (Monkhouse, *Drug Development and Industrial Pharmacy*, 1984, 10(8-9), 1373-412.) On the other hand, bound water is not available if it is a crystal hydrate, hydrogen bonded, or sorbed or trapped in an amorphous structure.

Hygroscopicity can be defined using various parameters. For example, hygroscopicity may be classified as shown in the following table. Callahan et al. (*Drug Development and Industrial Pharmacy*, 1982, 8(3), 355-69).

Class 1: Non-hygroscopic	Essentially no moisture increases occur at RH <90%
Class 2: Slightly hygroscopic	Essentially no moisture increases occur at RH <90%
Class 3: Moderately hygroscopic	Moisture content increase \leq 5% after storage for 1 week at RH <60%
Class 4: Very hygroscopic	Moisture content increase may occur at RH as low as 40-50%

Alternatively, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has defined hygroscopicity, based on the static method, after storage at 25° C. for 24 hours at 80% RH.

Classification	Increase in mass after 24 h at 25° C. and 80% RH
Slightly hygroscopic	<2% and \geq 0.2%
Hygroscopic	<15% and \geq 0.2%
Very hygroscopic	\geq 15%
Deliquescent	Forms a liquid

It is highly desirable to have a crystalline form of a therapeutic agent that is neither hygroscopic nor deliquescent. Stable, non-hygroscopic salts facilitate the production of solid pharmaceutical compositions. Hygroscopicity of active pharmaceutical ingredients can cause a number of downstream problems including a lack of storability, agglomeration, and inadequate flowability during formulating and processing. Hygroscopic formulations may exhibit poor tabletability which can make the manufacture of orally administrable dosage forms problematic.

The salts of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine of the present invention are non-hygroscopic. Because of their stability to moisture they are suitable for active pharmaceutical ingredient storage, for preparing bulk pharmaceutical compositions, and for manufacturing orally administrable solid-dosage forms that are useful for, inter alia, weight management.

One aspect of the present invention pertains to dosage forms comprising a therapeutically effective amount of a salt selected from: a pharmaceutically acceptable salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and pharmaceutically acceptable solvates and hydrates thereof, wherein the dosage form is a non-hygroscopic dosage form.

In some embodiments, the salt absorbs less than about 2% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 1% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.6% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.5% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.4% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.3% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.2% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs less than about 0.1% water by weight after about 2 h at about 90% RH and about 25° C.

In some embodiments, the salt absorbs: less than about 2% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 1% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 0.6% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 0.5% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 0.4% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 0.3% water by weight after about 2 h at about 90% RH and about 25° C.; less than about 0.2% water by weight

In some embodiments, the salt absorbs from about 0.6% to about 0.5% water by weight after about 2 h at about 90% RH and about 25° C.

One aspect of the present invention pertains to dosage forms comprising a therapeutically effective amount of (R)-

37

8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt or a crystalline form thereof.

In some embodiments, the dosage form further comprises one or more pharmaceutically acceptable excipients.

One aspect of the present invention pertains to dosage forms for oral administration to an individual in need of weight management.

In some embodiments, the weight management comprises weight loss.

In some embodiments, the weight management comprises maintenance of weight loss.

In some embodiments, the weight management comprises decreased food consumption.

In some embodiments, the weight management comprises increasing meal-related satiety.

In some embodiments, the weight management comprises reducing pre-meal hunger.

In some embodiments, the weight management comprises reducing intra-meal food intake.

In some embodiments, the weight management further comprises a reduced-calorie diet.

In some embodiments, the weight management further comprises a program of regular exercise.

In some embodiments, the weight management further comprises both a reduced-calorie diet and a program of regular exercise.

In some embodiments, the individual in need of weight management is an obese patient with an initial body mass index ≥ 30 kg/m².

In some embodiments, the individual in need of weight management is an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the weight related co-morbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the dosage form is for administration in combination with phentermine.

Indications

Obesity is a life-threatening disorder in which there is an increased risk of morbidity and mortality arising from concomitant diseases such as, but not limited to, type II diabetes, hypertension, stroke, certain forms of cancers and gallbladder disease.

Obesity has become a major healthcare issue in the Western World and increasingly in some third world countries. The increase in the number of obese people is due largely to the increasing preference for high fat content foods but also, and this can be a more important factor, the decrease in activity in most people's lives. In spite of the growing awareness of the health concerns linked to obesity the percentage of individuals that are overweight or obese continues to increase. The most significant concern, from a public health perspective, is that children who are overweight grow up to be overweight or obese adults, and accordingly are at greater risk for major health problems. Therefore, it appears that the number of individuals that are overweight or obese will continue to increase.

Whether someone is classified as overweight or obese is generally determined on the basis of his or her body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m²). Thus, the units for BMI are kg/m². BMI is more highly correlated with body fat than any other indicator of height and weight. A person is considered overweight when they have a BMI in the range of 25-30 kg/m², whereas a person with a BMI over 30 kg/m² is classified as obese. Obesity is further divided into three classes: Class I

38

(BMI of about 30 to about 34.9 kg/m²), Class II (BMI of about 35 to 39.9 kg/m²) and Class III (about 40 kg/m² or greater); see Table below for complete classifications.

Classification of Weight by Body Mass Index (BMI)

BMI	CLASSIFICATION
<18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Obesity (Class I)
35.0-39.9	Obesity (Class II)
>40	Extreme Obesity (Class III)

As the BMI increases for an individual there is an increased risk of morbidity and mortality relative to an individual with normal BMI. Accordingly, overweight and obese individuals (BMI of about 25 kg/m² and above) are at increased risk for physical ailments such as, but not limited to, high blood pressure, cardiovascular disease (particularly hypertension), high blood cholesterol, dyslipidemia, type II (non-insulin dependent) diabetes, insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, angina pectoris, congestive heart failure, stroke, gallstones, cholecystitis and cholelithiasis, gout, osteoarthritis, obstructive sleep apnea and respiratory problems, some types of cancer (such as endometrial, breast, prostate, and colon), complications of pregnancy, poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation), diseases of reproduction (such as sexual dysfunction, both male and female, including male erectile dysfunction), bladder control problems (such as stress incontinence), uric acid nephrolithiasis, psychological disorders (such as depression, eating disorders, distorted body image, and low self esteem). Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing other ailments, such as, but not limited to, coronary heart disease.

As mentioned above, obesity increases the risk of developing cardiovascular diseases. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complications induced by obesity. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for type 2 diabetes and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of obesity [Perry, I. J., et al. *BMJ* 310, 560-564 (1995)]. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%.

Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous-system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina and increases the risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain

and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.

The first line of treatment for individuals that are overweight or obese is to offer diet and life style advice, such as, reducing the fat content of their diet and increasing their physical activity. However many patients find these difficult to maintain and need additional help from drug therapy to sustain results from these efforts.

Most currently marketed products have been unsuccessful as treatments for obesity owing to a lack of efficacy or unacceptable side-effect profiles. The most successful drug so far was the indirectly acting 5-hydroxytryptamine (5-HT) agonist d-fenfluramine (Redux™) but reports of cardiac valve defects in up to one third of the patient population led to its withdrawal by the FDA in 1998.

The 5-HT_{2C} receptor is recognized as a well-accepted receptor target for the treatment of obesity, psychiatric, and other disorders. See, for example, Halford et al., *Serotonergic Drugs Effects on Appetite Expression and Use for the Treatment of Obesity*, Drugs 2007; 67 (1): 27-55; Naughton et al., *A Review Of The Role Of Serotonin Receptors In Psychiatric Disorders*. Human Psychopharmacology (2000), 15(6), 397-415.

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (lorcaserin hydrochloride) is an agonist of the 5-HT_{2C} receptor and shows effectiveness at reducing obesity in animal models and humans. In a phase 3 human clinical trial evaluating the safety and efficacy of lorcaserin for weight management, statistical significance ($p < 0.0001$) was achieved on all three of the hierarchically ordered co-primary endpoints for patients treated with lorcaserin versus placebo. Treatment with lorcaserin was generally very well tolerated. An assessment of echocardiograms indicated no apparent drug-related effect on the development of US Food and Drug Administration (FDA)-defined valvulopathy over the two-year treatment period. The hierarchically ordered endpoints were the proportion of patients achieving 5% or greater weight loss after 12 months, the difference in mean weight loss compared to placebo after 12 months, and the proportion of patients achieving 10% or greater weight loss after 12 months. Compared to placebo, using an intent-to-treat last observation carried forward (ITT-LOCF) analysis, treatment with lorcaserin was associated with highly statistically significant ($p < 0.0001$) categorical and average weight loss from baseline after 12 months: 47.5% of lorcaserin patients lost greater than or equal to 5% of their body weight from baseline compared to 20.3% in the placebo group. This result satisfied the efficacy benchmark in the most recent FDA draft guidance. Average weight loss of 5.8% of body weight, or 12.7 pounds, was achieved in the lorcaserin group, compared to 2.2% of body weight, or 4.7 pounds, in the placebo group. Statistical separation from placebo was observed by Week 2, the first post-baseline measurement. 22.6% of lorcaserin patients lost greater than or equal to 10% of their body weight from baseline, compared to 7.7% in the placebo group. Lorcaserin patients who completed 52 weeks of treatment according to the protocol lost an average of 8.2% of body weight, or 17.9 pounds, compared to 3.4%, or 7.3 pounds, in the placebo group ($p < 0.0001$).

In addition, the 5-HT_{2C} receptor is also involved in other diseases, conditions and disorders, such as, obsessive compulsive disorder, some forms of depression, and epilepsy. Accordingly, 5-HT_{2C} receptor agonists can have anti-panic properties, and properties useful for the treatment of sexual dysfunction. In addition, 5-HT_{2C} receptor agonists are useful for the treatment of psychiatric symptoms and behaviors in individuals with eating disorders such as, but not limited to,

anorexia nervosa and bulimia nervosa. Individuals with anorexia nervosa often demonstrate social isolation. Anorexic individuals often present symptoms of being depressed, anxious, obsession, perfectionistic traits, and rigid cognitive styles as well as sexual disinterest. Other eating disorders include, anorexia nervosa, bulimia nervosa, binge eating disorder (compulsive eating) and ED-NOS (i.e., eating disorders not otherwise specified—an official diagnosis). An individual diagnosed with ED-NOS possess atypical eating disorders including situations in which the individual meets all but a few of the criteria for a particular diagnosis. What the individual is doing with regard to food and weight is neither normal nor healthy.

The 5-HT_{2C} receptor plays a role in Alzheimer Disease (AD). Therapeutic agents currently prescribed for Alzheimer's disease (AD) are cholinomimetic agents that act by inhibiting the enzyme acetylcholinesterase. The resulting effect is increased levels of acetylcholine, which modestly improves neuronal function and cognition in patients with AD. Although, dysfunction of cholinergic brain neurons is an early manifestation of AD, attempts to slow the progression of the disease with these agents have had only modest success, perhaps because the doses that can be administered are limited by peripheral cholinergic side effects, such as tremors, nausea, vomiting, and dry mouth. In addition, as AD progresses, these agents tend to lose their effectiveness due to continued cholinergic neuronal loss.

Therefore, there is a need for agents that have beneficial effects in AD, particularly in alleviating symptoms by improving cognition and slowing or inhibiting disease progression, without the side effects observed with current therapies. Therefore, serotonin 5-HT_{2C} receptors, which are exclusively expressed in brain, are attractive targets.

Another disease, disorder or condition that can be associated with the function of the 5-HT_{2C} receptor is erectile dysfunction (ED). Erectile dysfunction is the inability to achieve or maintain an erection sufficiently rigid for intercourse, ejaculation, or both. An estimated 20-30 million men in the United States have this condition at some time in their lives. The prevalence of the condition increases with age. Five percent of men 40 years of age report ED. This rate increases to between 15% and 25% by the age of 65, and to 55% in men over the age of 75 years.

Erectile dysfunction can result from a number of distinct problems. These include loss of desire or libido, the inability to maintain an erection, premature ejaculation, lack of emission, and inability to achieve an orgasm. Frequently, more than one of these problems presents themselves simultaneously. The conditions may be secondary to other disease states (typically chronic conditions), the result of specific disorders of the urogenital system or endocrine system, secondary to treatment with pharmacological agents (e.g. anti-hypertensive drugs, antidepressant drugs, antipsychotic drugs, etc.) or the result of psychiatric problems. Erectile dysfunction, when organic, is primarily due to vascular irregularities associated with atherosclerosis, diabetes, and hypertension.

There is evidence for use of a serotonin 5-HT_{2C} agonist for the treatment of sexual dysfunction in males and females. The serotonin 5-HT_{2C} receptor is involved with the processing and integration of sensory information, regulation of central monoaminergic systems, and modulation of neuroendocrine responses, anxiety, feeding behavior, and cerebrospinal fluid production [Tecott, L. H., et al. *Nature* 374: 542-546 (1995)]. In addition, the serotonin 5-HT_{2C} receptor has been implicated in the mediation of penile erections in rats, monkeys, and humans.

In summary, the 5-HT_{2C} receptor is a validated and well-accepted receptor target for the prophylaxis and/or treatment of 5-HT_{2C} mediated receptor diseases and disorders, such as, obesity, eating disorders, psychiatric disorders, Alzheimer Disease, sexual dysfunction and disorders related thereto. It can be seen that there exists a need for selective 5-HT_{2C} receptor agonists that can safely address these needs. The present invention is directed to these, as well as other, important ends.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

In some embodiments, the weight management comprises weight loss.

In some embodiments, the weight management comprises maintenance of weight loss.

In some embodiments, the weight management comprises decreased food consumption.

In some embodiments, the weight management comprises increasing meal-related satiety.

In some embodiments, the weight management comprises reducing pre-meal hunger.

In some embodiments, the weight management comprises reducing intra-meal food intake.

In some embodiments, the weight management further comprises a reduced-calorie diet.

In some embodiments, the weight management further comprises a program of regular exercise.

In some embodiments, the weight management further comprises both a reduced-calorie diet and a program of regular exercise.

In some embodiments, the individual in need of weight management is an obese patient with an initial body mass index ≥ 30 kg/m².

In some embodiments, the individual in need of weight management is an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management is an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 30 kg/m².

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 27 kg/m².

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 25 kg/m².

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related comorbid condition

selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 20 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 20 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 21 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 21 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 22 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 22 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 23 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 23 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 24 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 24 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 25 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 25 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 26 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual in need of weight management has an initial body mass index \geq about 26 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for the treatment of obesity, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

In some embodiments, the method for the treatment of obesity further comprises the administration or prescription of phentermine.

In some embodiments, the method for the treatment of obesity further comprises gastric electrical stimulation.

One aspect of the present invention pertains to methods for inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual in preparation of the individual for bariatric surgery, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual following bariatric surgery, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for inducing satiety in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for decreasing food intake in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for decreasing hunger in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for decreasing food cravings in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for increasing intermeal interval in an individual, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

One aspect of the present invention pertains to methods for the treatment of a disorder selected from: schizophrenia, anxiety, depression, psychoses and alcohol addiction, com-

prising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

In some embodiments, the disorder is schizophrenia.

In some embodiments, the disorder is anxiety.

In some embodiments, the disorder is depression.

In some embodiments, the disorder is psychoses.

In some embodiments, the disorder is alcohol addiction.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for weight management in an individual.

In some embodiments, the weight management comprises weight loss.

In some embodiments, the weight management comprises maintenance of weight loss.

In some embodiments, the weight management comprises decreased food consumption.

In some embodiments, the weight management comprises increasing meal-related satiety.

In some embodiments, the weight management comprises reducing pre-meal hunger.

In some embodiments, the weight management comprises reducing intra-meal food intake.

In some embodiments, the weight management further comprises a reduced-calorie diet.

In some embodiments, the weight management further comprises a program of regular exercise.

In some embodiments, the weight management further comprises both a reduced-calorie diet and a program of regular exercise.

In some embodiments, the individual is an obese patient with an initial body mass index ≥ 30 kg/m².

In some embodiments, the individual is an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual is an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual has an initial body mass index ≥ 30 kg/m².

In some embodiments, the individual has an initial body mass index ≥ 27 kg/m².

In some embodiments, the individual has an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual has an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the individual has an initial body mass index ≥ 25 kg/m².

In some embodiments, the individual has an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related comorbid condition.

In some embodiments, the individual has an initial body mass index ≥ 25 kg/m² in the presence of at least one weight related comorbid condition selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the medicament for weight management is used in combination with phentermine.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for a disorder related to 5-HT_{2C} receptor activity in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for the treatment of obesity in an individual.

In some embodiments, the treatment of obesity further comprises the administration or prescription of phentermine.

In some embodiments, the treatment of obesity further comprises gastric electrical stimulation.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual in preparation of the individual for bariatric surgery.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual following bariatric surgery.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for inducing satiety in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for decreasing food intake in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for decreasing hunger in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for decreasing food cravings in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for increasing intermeal interval in an individual.

One aspect of the present invention pertains to the use of salts of the present invention, in the manufacture of a medicament for the treatment of a disorder selected from: schizophrenia, anxiety, depression, psychoses and alcohol addiction in an individual.

In some embodiments, the disorder is schizophrenia.

In some embodiments, the disorder is anxiety.

In some embodiments, the disorder is depression.

In some embodiments, the disorder is psychoses.

In some embodiments, the disorder is alcohol addiction.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of treatment of a disorder related to 5-HT_{2C} receptor activity in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of treatment of obesity in an individual.

In some embodiments, the method of treatment of obesity further comprises the administration or prescription of phentermine.

In some embodiments, the method of treatment of obesity further comprises gastric electrical stimulation.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of inducing weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual in preparation of the individual for bariatric surgery.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of maintaining weight loss, BMI loss, waist circumference loss or body fat percentage loss in an individual following bariatric surgery.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of inducing satiety in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of decreasing food intake in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of decreasing hunger in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of decreasing food cravings in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of increasing intermeal interval in an individual.

One aspect of the present invention pertains to salts and pharmaceutical compositions of the present invention, for use in a method of treatment of a disorder selected from: schizophrenia, anxiety, depression, psychoses and alcohol addiction in an individual.

In some embodiments, the disorder is schizophrenia.

In some embodiments, the disorder is anxiety.

In some embodiments, the disorder is depression.

In some embodiments, the disorder is psychoses.

In some embodiments, the disorder is alcohol addiction.

One aspect of the present invention pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, a pharmaceutical composition, or a dosage form of the present invention.

In some embodiments, the weight management comprises one or more of: weight loss, maintenance of weight loss, decreased food consumption, increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

In some embodiments, the weight management is as an adjunct to diet and exercise.

In some embodiments, the individual in need of weight management is selected from: an obese patient with an initial body mass index ≥ 30 kg/m²; an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition; an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition; wherein the weight related co-morbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the method further comprises administering a second anti-obesity agent to the individual.

In some embodiments, the second anti-obesity agent is selected from: chlorphentermine, clortermine, phenpentermine, and phentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the method further comprises administering an anti-diabetes agent to the individual.

In some embodiments, the anti-diabetes agent is metformin.

One aspect of the present invention pertains to uses of a salt of the present invention, in the manufacture of a medicament for weight management in an individual.

In some embodiments, the weight management comprises one or more of: weight loss, maintenance of weight loss, decreased food consumption, increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

In some embodiments, the medicament is used as an adjunct to diet and exercise.

In some embodiments, the individual in need of weight management is selected from:

an obese patient with an initial body mass index ≥ 30 kg/m²; an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition; and an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition; wherein the weight related comorbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

In some embodiments, the medicament is used in combination with a second anti-obesity agent.

In some embodiments, the second anti-obesity agent is selected from: chlorphentermine, clortermine, phenpentermine, and phentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the medicament is used in combination with an anti-diabetes agent.

In some embodiments, the medicament is used in combination with an anti-diabetes agent; wherein the anti-diabetes agent is metformin.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management; wherein the weight management comprises one or more of: weight loss, maintenance of weight loss, decreased food consumption, increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use as an adjunct to diet and exercise for weight management.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management; wherein the individual in need of weight management is selected from: an obese patient with an initial body mass index ≥ 30 kg/m²; an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight

related comorbid condition; and an overweight patient with an initial body mass index ≥ 27 kg/m² in the presence of at least one weight related comorbid condition; wherein the weight related co-morbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management in combination with a second anti-obesity agent.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management in combination with a second anti-obesity agent selected from: chlorphentermine, clortermine, phenpentermine, and phentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

One aspect of the present invention pertains to salts, pharmaceutical compositions, and dosage forms of the present invention, for use in a method of weight management in combination with an anti-diabetes agent; wherein the anti-diabetes agent is metformin.

Combination Therapies

The salts of the present invention can be used in combination with suitable pharmaceutical agents.

In some embodiments the salts of the present invention can be used in combination with a second anti-obesity agent. Anti-obesity agents include, for example, adrenergic reuptake inhibitors, apolipoprotein-B secretion/microsomal triglyceride transfer protein inhibitors, $\beta 3$ adrenergic receptor agonists, bombesin agonists, cannabinoid 1 receptor antagonists, cholecystokinin-A agonists, ciliary neurotrophic factors, dopamine agonists, galanin antagonists, ghrelin receptor antagonists, glucagon-like peptide-1 receptor agonists, glucocorticoid receptor agonists or antagonists, histamine-3 receptor antagonists or reverse agonists, human agouti-related proteins, leptin receptor agonists, lipase inhibitors, MCR-4 agonists, melanin concentrating hormone antagonists, melanocyte-stimulating hormone receptor analogs, monoamine reuptake inhibitors, neuromedin U receptor agonists, neuropeptide-Y antagonists, orexin receptor antagonists, stimulants, sympathomimetic agents, thyromimetic agents, and urocortin binding protein antagonists.

In some embodiments, the second anti-obesity agent is selected from: 4-methylamphetamine, 5-HTP, amfecloral, amfepramorex, amfepramone, aminorex, amphetamine, amphetaminil, atomoxetine, benfluorex, benzphetamine, bromocriptine, bupropion, cathine, cathinone, cetilistat, chlorphentermine, ciclazindol, clobenzorex, cloforex, clominox, clortermine, dapiclermin, dehydroepiandrosterone, dehydroepiandrosterone analogues, dexamethylphenidate, dextroamphetamine, dextromethamphetamine, difemetorex, dimethylcathinone, dinitrophenol, diphemethoxidine, ephedra, ephedrine, ethylamphetamine, etolorex, fenbutrazate, fencamfamine, fenethylamine, fenproporex, fludorex, fluminorex, furfenorex, galactomannan, glucomannan, ibipinabant, indanorex, khat, L-dopa, leptin, a leptin analog, levopropylhexedrine, lisdexamfetamine, L-phenylalanine, L-tryptophan, L-tyrosine, N-[[trans-4-[(4,5-dihydro[1]benzothiepin-5,4-d]thiazol-2-yl)amino]cyclohexyl]methyl]methanesulfonamide, manifaxine, mazindol, mefenorex, metformin, methamphetamine, methylphenidate, naloxone, naltrexone, oleoyl-estrone, orlistat, otenabant, oxyntomodulin, P57, pemoline, peptide YY, phendimetrazine, phenethylamine, phenmetrazine, phenpentermine, phentermine, phenylpropanolamine, pipradrol, prolintane, propylhexedrine, pseudoephedrine, pyrovalerone, radafaxine, reboxetine,

51

rimonabant, setazindol, sibutramine, simmondsin, sterculia, surinabant, synephrine, taranabant, tesofensine, topiramate, viloxazine, xylopropamine, yohimbine, zonisamide, and zylofuramine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the second anti-obesity agent is selected from: 4-methylamphetamine, amfecloral, amfepramone, aminorex, amphetamine, amphetaminil, atomoxetine, benfluorex, benzphetamine, bupropion, cathine, cathinone, chlorphentermine, ciclazindol, clobenzorex, cloforex, clominox, clortermine, dexamethylphenidate, dextroamphetamine, dextromethamphetamine, difemetorex, dimethylcathinone, diphemethoxidine, ephedra, ephedrine, ethylamphetamine, etolorex, fenbutrazate, fencamfamine, fenethylamine, fenproporex, fludorex, fluminorex, fufenorex, indanorex, khat, levopropylhexedrine, lisexamfetamine, manifaxine, mazindol, mfenorex, methamphetamine, methylphenidate, pemoline, phendimetrazine, phenethylamine, phenmetrazine, phenpentermine, phentermine, phenylpropanolamine, pipradrol, prolintane, propylhexedrine, pseudoephedrine, pyrovalerone, radafaxine, setazindol, sibutramine, synephrine, taranabant, tesofensine, viloxazine, xylopropamine, and zylofuramine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, the second anti-obesity agent is selected from: chlorphentermine, clortermine, phenpentermine, and phentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments the salts of the present invention can be used in combination with an anti-diabetes agent. Anti-diabetes agents include, for example, DPP-IV inhibitors, biguanides, alpha-glucosidase inhibitors, insulin analogues, sulfonylureas, SGLT2 inhibitors, meglitinides, thiazolidinediones, anti-diabetic peptide analogues, and GPR119 agonists.

In some embodiments, the anti-diabetes agent is selected from: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, phenformin, metformin, buformin, proguanil, acarbose, miglitol, voglibose, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glibenclamide, glimepiride, gliclazide, dapagliflozin, remigliflozin, sergliflozin, and 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxy-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

In some embodiments, the anti-diabetes agent is a DPP-IV inhibitor selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: 3(R)-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one; 1-[2-(3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile; (1S,3S,5S)-2-[2(S)-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile; 2-[6-(3(R)-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile; 8-[3(R)-aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine; 1-[N-[3(R)-pyrrolidinyl]glycyl]pyrrolidin-2(R)-yl boronic acid; 4(S)-fluoro-1-[2-[(1R,3S)-3-(1H-1,2,4-triazol-1-ylmethyl)cyclopentylamino]acetyl]pyrrolidine-2(S)-carbonitrile; 1-[2(S,3S,11bS)-2-amino-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl]-4(S)-(fluoromethyl)pyrrolidin-2-one; (2S,4S)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethylamino]acetylpyrrolidine; 8-(cis-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-3-methyl-7-(3-methyl-but-2-enyl)-1-(2-oxo-2-phenylethyl)-3,7-dihydro-purine-2,6-dione; 1-[(3S,4S)-4-amino-1-(4-(3,3-

52

difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one; (R)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile; 5-[(S)-2-[2-((S)-2-cyanopyrrolidin-1-yl)-2-oxo-ethylamino]-propyl]-5-(1H-tetrazol-5-yl)10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide; ((2S,4S)-4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone; (2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile; 6-[3(R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione; 2-{6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl}-4-fluorobenzonitrile; (2S)-1-[[2-(5-methyl-2-phenyloxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile; (2S)-1-[[1,1-dimethyl-3-(4-pyridin-3-ylimidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile; (3,3-difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone; (2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile; (2S,5R)-5-ethynyl-1-[N-(4-methyl-1-(4-carboxy-pyridin-2-yl)piperidin-4-yl)glycyl]pyrrolidine-2-carbonitrile; and (1S,6R)-3-[[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]carbonyl]-6-(2,4,5-trifluorophenyl)cyclohex-3-en-1-amine.

In some embodiments, the anti-diabetes agent is an alpha-glucosidase inhibitor selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: (2R,3R,4R,5R)-4-((2R,3R,4R,5S,6R)-5-((2R,3R,4S,5S,6R)-3,4-dihydroxy-6-methyl-5-((1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylammonotetrahydro-2H-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-2,3,5,6-tetrahydroxyhexanal; (2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol; and (1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol.

In some embodiments, the anti-diabetes agent is a sulfonylurea selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: N-(4-(N-(cyclohexylcarbonyl)sulfamoyl)phenethyl)-5-methylpyrazine-2-carboxamide; 5-chloro-N-(4-(N-(cyclohexylcarbonyl)sulfamoyl)phenethyl)-2-methoxybenzamide; and 3-ethyl-4-methyl-N-(4-(N-((1R,4R)-4-methylcyclohexylcarbonyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide.

In some embodiments, the anti-diabetes agent is an SGLT2 inhibitor selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol; ethyl((2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(4-(4-isopropoxybenzyl)-1-isopropyl-5-methyl-1H-pyrazol-3-yloxy)tetrahydro-2H-pyran-2-yl)methyl carbonate; and ethyl((2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(2-(4-methoxybenzyl)phenoxy)tetrahydro-2H-pyran-2-yl)methyl carbonate.

In some embodiments, the anti-diabetes agent is a meglitinide selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: (S)-2-ethoxy-4-(2-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butylamino)-2-oxoethyl)benzoic acid; (R)-2-((1R,4R)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid; and (S)-2-benzyl-4-((3aR,7aS)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)-4-oxobutanoic acid.

53

In some embodiments, the anti-diabetes agent is a biguanide selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof: metformin, phenformin, buformin, and proguanil.

In some embodiments, the anti-diabetes agent is metformin.

In some embodiments, the anti-diabetes agent is a GPR119 agonist selected from the GPR119 agonists disclosed in the following PCT applications: WO2006083491, WO2008081204, WO2009123992, WO2010008739, WO2010029089, and WO2010149684.

In some embodiments, the anti-diabetes agent is 4-[6-(6-methanesulfonyl-2-methyl-pyridin-3-ylamino)-5-methoxypyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester.

In some embodiments, the anti-diabetes agent is 5-(4-(3-fluoro-4-(methylsulfonyl)phenoxy)butan-2-yl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole.

Other anti-obesity agents, and anti-diabetes agents including the agents set forth *infra*, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art. It will be understood that the scope of combination therapy of the salts of the present invention with other anti-obesity agents and with anti-diabetes agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight, obese, and diabetic individuals.

One aspect of the present invention pertains to salts of the present invention, characterized in that the salts is administered in conjunction with a second anti-obesity agent as described herein.

One aspect of the present invention pertains to salts of the present invention, characterized in that the salt is administered in conjunction with an anti-diabetes agent as described herein.

One aspect of the present invention pertains to salts of the present invention for use in combination with a second anti-obesity agent for use in weight management.

One aspect of the present invention pertains to salts of the present invention for use in combination with an anti-diabetes agent for use in weight management and the treatment of diabetes.

One aspect of the present invention pertains to methods of weight management in an individual in need thereof, comprising administering to the individual a salt of the present invention and a second anti-obesity agent wherein the salt and the second anti-obesity agent are administered to the individual simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of weight management and treating diabetes in an individual in need thereof, comprising administering to the individual a salt of the present invention and an anti-diabetes agent wherein the salt and the anti-diabetes agent are administered to the individual simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of weight management in an individual in need thereof, wherein the individual has been or is being treated with a second anti-obesity agent, the method comprising administering to the individual a therapeutically effective amount of a salt of the present invention.

One aspect of the present invention pertains to methods of weight management and treatment of diabetes in an individual in need thereof, wherein the individual has been or is being treated with an anti-diabetes agent, the method comprising administering to the individual a therapeutically effective amount of a salt of the present invention.

54

One aspect of the present invention pertains to anti-obesity agents, characterized in that the anti-obesity agent is administered in conjunction with a salt of the present invention.

One aspect of the present invention pertains to anti-diabetes agents, characterized in that the anti-diabetes agent is administered in conjunction with a salt of the present invention.

One aspect of the present invention pertains to anti-obesity agents for use in combination with a salt of the present invention for use in weight management.

One aspect of the present invention pertains to anti-diabetes agents for use in combination with a salt of the present invention for use in weight management and the treatment of diabetes.

One aspect of the present invention pertains to methods of weight management in an individual in need thereof, comprising administering to the individual an anti-obesity agent and a salt of the present invention wherein the anti-obesity agent and the salt are administered to the individual simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of weight management and treating diabetes in an individual in need thereof, comprising administering to the individual an anti-diabetes agent and a salt of the present invention wherein the anti-diabetes agent and the salt are administered to the individual simultaneously, separately, or sequentially.

One aspect of the present invention pertains to methods of weight management in an individual in need thereof, wherein the individual has been or is being treated with a salt of the present invention, the method comprising administering to the individual a therapeutically effective amount of a second anti-obesity agent.

One aspect of the present invention pertains to methods of weight management and treatment of diabetes in an individual in need thereof, wherein the individual has been or is being treated with a salt of the present invention, the method comprising administering to the individual a therapeutically effective amount of an anti-diabetes agent.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds and salts thereof described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version 7.0.1, AutoNom version 2.2, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Powder X-ray Diffraction (PXRD) studies were conducted using an X'Pert PRO MPD powder diffractometer (PANalytical, Inc.; EQ0233) with a Cu source set at 45 kV and 40 mA, Cu(K α) radiation and an X'Celerator detector. Samples were placed on a PXRD sample plate either as-is or ground slightly to reduce the size of large particles or crystals. Data were collected with the samples spinning from 5° to 40° 2 θ . Data were analyzed by X'Pert Data Viewer software, version 1.0a, to determine crystallinity and/or crystal form, and by X'Pert HighScore software, version 1.0b, to generate the tables of PXRD peaks.

55

Differential scanning calorimetry (DSC) studies were conducted using a TA Instruments, Q2000 (EQ1980) at heating rate 10° C./min. The instruments were calibrated by the vendor for temperature and energy using the melting point and enthalpy of fusion of an indium standard.

Thermogravimetric analyses (TGA) were conducted using a TA Instruments TGA Q5000 (EQ1982) at heating rate 10° C./min. The instrument was calibrated by the vendor using Alumel and Nickel Curie points for the furnace temperature and a standard weight for the balance.

Dynamic moisture-sorption (DMS) studies were conducted using a dynamic moisture-sorption analyzer, VTI Corporation, SGA-100, equipment #0228. Samples were prepared for DMS analysis by placing 5 mg to 20 mg of a sample in a tared sample holder. The sample was placed on the hang-down wire of the VTI balance. A drying step was run, typically at 40° C. and 0.5-1% RH for 1-2 h. The isotherm temperature is 25° C. Defined % RH holds typically ranged from 10% RH to 90% RH or 95% RH, with intervals of 10 to 20% RH. A % weight change smaller than 0.010% over a specified number of minutes (typically 10-20), or up to 2 h, whichever occurs first, is required before continuing to the next % RH hold. The water content of the sample equilibrated as described above was determined at each % RH hold.

If saturated in water with excess solid, a deliquescent compound or salt thereof equilibrated in a closed system at a given temperature produces a % RH in that closed system that is equal to its deliquescent % RH (DRH) at that temperature. Fractional relative humidity is equal to water activity (a_w) in the vapor phase and at equilibrium in a closed system, the a_w in an aqueous solution is equal to the a_w in the vapor phase above the solution (see Equation 1).

$$\frac{DRH}{100\%} = \frac{\% RH}{100\%} (\text{above enclosed sat aq sol'n at equil}) = a_w(\text{vapor}) = a_w(\text{liquid}) \quad \text{Equation 1}$$

A water activity meter was used to measure DRH for selected salts described herein. The instrument used for this study is a Decagon Devices AquaLab 4TE water activity meter, equipment #2169. This instrument is designed with temperature control and a small headspace above the enclosed sample to establish equilibrium between solution and vapor phases quickly. Measured a_w values at 25° C. for samples of aqueous-saturated Compound 1 salts with excess solid were multiplied by 100% to get DRH values in % RH.

Acquity ultra performance liquid chromatography (UPLC) from Waters was used for solubility and stoichiometry determination. Instrument number is SY-EQ 1889. UPLC was equipped with Acquity PDA detector. UPLC mobile phase solvent A was 0.1% TFA in DI-water, solvent B was 0.1% TFA in acetonitrile. The mobile phase gradient as shown in the table below:

Time (min)	Flow (mL/min)	% A	% B	Curve
	0.600	95.0	5.0	
2.00	0.600	5.0	95.0	6
2.50	0.600	5.0	95.0	6
2.75	0.600	95.0	5.0	1
5.00	0.000	95.0	5.0	11

Column temperature was 40±5° C. Acquity UPLC® HSS T3 1.8 µm, 2.1x50 mm column was used.

56

A known amount of sample was dissolved in water and analyzed by UPLC. The weight percent of Compound 1 in the salt samples was determined by comparing the UV signal to that of a standard, Compound 1 hydrochloride salt hemihydrate, or Compound 1 free base. The percentage of Compound 1 or the percentage of the counterion determined was compared to the theoretical values to establish the stoichiometry.

Example 1

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Hemi-edisylate Salt (Compound 1 Hemi-edisylate Salt, Form I)

The title salt was prepared by the dropwise addition of 0.5 equivalents of aqueous 1,2-ethanedithiolonic acid dihydrate (~3.7 M) to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine free base in either acetonitrile or isopropyl acetate with vigorous stirring. Immediate precipitation was observed. The solid obtained was washed with isopropyl alcohol and allowed to dry on the filter.

The title salt was an anhydrous crystalline material with a melting onset of ~298° C. It was non-hygroscopic by DMS analysis, picking up just 0.14% weight out to and including the 95% RH hold at 25° C. The DRH was determined by water activity measurement of saturated aqueous solution with excess solid to be 99.7% RH at 25° C., which indicated that the title salt was not deliquescent.

A known amount of the title salt was dissolved in water and analyzed by UPLC. The amount of Compound 1 in sample was determined to be 68.2%. This is in good agreement with the theoretical value, 67.3%. The solubility of the title salt in water was determined by UPLC to be 61 mg/mL, with a final pH of 6.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 1. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 2. DMS analysis of the title salt is shown in FIG. 3.

Example 2

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Phosphate Salt (Compound 1 Phosphate Salt, Form I)

The title salt was prepared by dropwise addition of orthophosphoric acid (85%) (0.5-1 mole equivalent) to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine free base in isopropyl acetate or acetonitrile with vigorous stirring. Immediate precipitation was observed in all experiments. Initially amorphous material was slurried in acetone; initially crystalline material was slurried/ripened in n-propanol for 3 days.

The title salt was a 1:1 salt based on stoichiometry determination. The melting onset by DSC was ~208° C. The TGA result for a crystalline sample prior to the n-propanol slurry is consistent with an anhydrous salt. It was non-hygroscopic, picking up 0.14% weight out to and including the 90% RH hold at 25° C. during DMS analysis. The title salt was non-deliquescent; the DRH by water activity measurement of a saturated solution in water with excess solid was 100% RH at 25° C.

A known amount of the title salt was dissolved in water and analyzed by UPLC. The amount of Compound 1 in the sample was 64.9%, slightly lower but in good agreement with

57

the theoretical amount, 66.6%. The solubility of the title salt, was 29.4 mg/mL, with a final pH of 4.6.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 4. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 5. DMS analysis of the title salt is shown in FIG. 6.

Example 3

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Citrate Salt Hemihydrate (Compound 1 Citrate Salt Hemihydrate, Form I)

The title salt was prepared by dropwise addition of 1 mole equivalent of citric acid in hot MeOH to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in isopropyl acetate. Precipitation occurred spontaneously. Attempts to prepare a hemicitrate salt resulted in oily products.

TGA data for the title salt, showed that it was solvated. The mass loss matches closely with a hemihydrate (observed 2.6%, theoretical 2.3%). The onset of dehydration is near 80° C. for the scan rate, 10° C./min.

The title salt lost only a small amount of its water of hydration during the drying step at 40° C. and ~1% RH for 1 h. It was not hygroscopic, picking up just 0.50% out to and including the 90% RH hold at 25° C., and not deliquescent. The DRH determined by water activity measurement of a saturated aqueous solution with excess solid was 100% RH at 25° C.

A known amount of the title salt was dissolved in water and analyzed by UPLC. The amount of Compound 1 in the sample was 53.2%. This is slightly higher than, but in fair agreement with the theoretical amount for a 1:1 citrate hemihydrate salt, 49.3%. The solubility in water was determined to be 33.9 mg/mL of the salt at a pH of 3.75.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 7. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 8. DMS analysis of the title salt is shown in FIG. 9.

Example 4

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Hemi-oxalate Salt (Compound 1 Hemi-oxalate Salt, Form I)

The title salt was prepared by dropwise addition of 1 mole equivalent of oxalic acid as a solid or as a solution in MeOH (~2.5 M) to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in isopropyl acetate. In each case the same crystal form was produced.

The title salt was anhydrous and displayed a melting onset temperature about 212° C. with weight loss by TGA starting just prior to the melting onset. The title salt was determined to be non-hygroscopic and non-deliquescent at 25° C. The DRH determined by water activity measurement of a saturated aqueous sample with excess solid was 100% RH (non-deliquescent) at 25° C.

A known amount of the title salt was dissolved in water and analyzed by UPLC. The amount of Compound 1 in the sample was 74.9%. The solid was slurried in cyclohexane and then analyzed a second time. The amount of Compound 1 in the second sample was 82.5%. The theoretical value for a hemi-oxalate salt of Compound 1 is 81.2%.

58

The solubility of the title salt, in water was determined by UPLC to be 23.3 mg/mL with a final pH 4.6.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 10. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 11. DMS analysis of the title salt is shown in FIG. 12.

Example 5

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Succinate Salt (Compound 1 Succinate Salt, Form I)

The title salt was prepared by the addition of succinic acid (0.5-1 eq.) in hot EtOH to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in isopropyl acetate. After overnight stirring, a solid was recovered by suction filtration and washed in isopropyl acetate.

The title salt showed a melting onset by DSC of 179.1° C. TGA showed no residual solvent, but did show apparent loss of the salt or component thereof prior to the melting onset.

The title salt was found to be non-hygroscopic by DMS analysis, picking up 0.07% weight out to and including the 90% RH hold at 25° C. It was non-deliquescent; DRH was measured by water activity determination for a saturated aqueous solution with excess solid to be 100.0% RH at 25° C.

A known amount of the title salt was dissolved in water and analyzed by UPLC. The amount of Compound 1 in the sample was 65-69%. This is slightly higher than theoretical, 62.4%, for a 1:1 salt, but much lower than the theoretical value for a hemisuccinate salt, 76.8%. Aqueous solubility of the title salt was 27.9 mg/mL, with a final pH 4.7.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 13. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 14. DMS analysis of the title salt is shown in FIG. 15.

Example 6

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Oxoglutarate Salt (Compound 1 Oxoglutarate Salt, Form I)

The title salt was prepared by addition of one equivalent of α -oxo-glutaric acid to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in ethyl acetate at 60° C. α -Oxo-glutaric acid in ethyl acetate at 60° C. was added dropwise with vigorous stirring. Precipitation occurred immediately and the suspension was allowed to cool and stir overnight. The resulting solid was recovered by filtration and air-dried in a fume hood overnight.

A known amount of Compound 1 oxoglutarate salt was dissolved in methanol and analyzed by UPLC. The percentage of Compound 1 in the salt sample was determined to be 59.7%. This is slightly higher than but in good agreement with the theoretical percentage of Compound 1 in an anhydrous Compound 1 oxoglutarate salt (57.3%).

The aqueous solubility of the title salt was determined by UPLC to be >65.1 mg/mL, with a final pH of 3.19.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 16. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 17. DMS analysis of the title salt is shown in FIG. 18.

Example 7

Preparation of Form I of (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Oxoglutarate Salt Solvate (Compound 1 Oxoglutarate Salt Solvate, Form I)

The title salt was prepared by addition of a molar equivalent of α -oxo-glutaric acid to a solution of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in acetonitrile at 60° C. α -Oxo-glutaric acid in acetonitrile at 60° C. was added dropwise with vigorous stirring. Precipitation occurred immediately and the suspension was allowed to cool and stir overnight. The resulting solid was recovered by filtration and air-dried in a fume hood overnight.

A known amount of Compound 1 oxoglutarate salt solvate was dissolved in methanol and analyzed by UPLC. The percentage of Compound 1 in the salt sample was determined to be 60.1%. This is slightly higher than the theoretical percentage Compound 1 in a solvate of Compound 1 oxoglutarate salt (54.%).

The aqueous solubility of Compound 1 oxoglutarate solvate was determined by UPLC to be >68.9 mg/mL, with a final pH of 3.21.

The powder X-ray diffraction pattern of the title salt is shown in FIG. 19. Thermal analysis (TGA and DSC) of the title salt is shown in FIG. 20. DMS analysis of the title salt is shown in FIG. 21.

Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

What is claimed is:

1. A salt selected from:

- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hem i-edisylate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 23.12°, 6.00°, and 19.70°, wherein the peaks can vary by ± 0.2 2θ ;
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 19.27°, 25.06°, and 25.77°, wherein the peaks can vary by ± 0.2 2θ ;
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 11.93°, 18.64°, and 24.52°, wherein the peaks can vary by ± 0.2 2θ ;
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hem i-oxalate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 6.34°, 21.69°, and 31.85°, wherein the peaks can vary by ± 0.2 2θ ;
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 27.62°, 20.65°, and 15.64°, wherein the peaks can vary by ± 0.2 2θ ; and
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 13.39°, 23.57°, and 21.22°, wherein the peaks can vary by ± 0.2 2θ ; and
- (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate, having an X-ray powder

der diffraction pattern comprising peaks, in terms of 2θ , at 26.02°, 11.53°, and 22.65°, wherein the peaks can vary by ± 0.2 2θ .

2. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemi-edisylate salt, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 23.12°, 6.00°, and 19.70°, wherein the peaks can vary by ± 0.2 2θ .

3. The salt according to claim 2, having an X-ray powder diffraction pattern as shown in FIG. 1, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

4. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine phosphate salt, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 19.27°, 25.06°, and 25.77°, wherein the peaks can vary by ± 0.2 2θ .

5. The salt according to claim 4, having an X-ray powder diffraction pattern as shown in FIG. 4, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

6. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine citrate salt hemihydrate, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 11.93°, 18.64°, and 24.52°, wherein the peaks can vary by ± 0.2 2θ .

7. The salt according to claim 6, having an X-ray powder diffraction pattern as shown in FIG. 7, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

8. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hem i-oxalate salt, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 6.34°, 21.69°, and 31.85°, wherein the peaks can vary by ± 0.2 2θ .

9. The salt according to claim 8, having an X-ray powder diffraction pattern as shown in FIG. 10, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

10. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine succinate salt, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 27.62°, 20.65°, and 15.64°, wherein the peaks can vary by ± 0.2 2θ .

11. The salt according to claim 10, having an X-ray powder diffraction pattern as shown in FIG. 13, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

12. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 13.39°, 23.57°, and 21.22°, wherein the peaks can vary by ± 0.2 2θ .

13. The salt according to claim 12, having an X-ray powder diffraction pattern as shown in FIG. 16, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

14. A salt that is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine oxoglutarate salt solvate, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 26.02°, 11.53°, and 22.65°, wherein the peaks can vary by ± 0.2 2θ .

15. The salt according to claim 14, having an X-ray powder diffraction pattern as shown in FIG. 19, wherein the peaks can vary by ± 0.2 2θ and the relative intensities of the peaks can vary.

61

16. A pharmaceutical composition comprising a salt according to claim 1, and a pharmaceutically acceptable carrier.

17. A process for preparing a pharmaceutical composition comprising admixing a salt according to claim 1, and a pharmaceutically acceptable carrier. 5

18. A dosage form comprising a therapeutically effective amount of a salt according to claim 1.

19. A method for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt according to claim 1. 10

20. The method according to claim 19, wherein said weight management comprises one or more of: weight loss, maintenance of weight loss, decreased food consumption, increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake. 15

21. The method according to claim 19, as an adjunct to diet and exercise.

22. The method according to claim 19, wherein said individual in need of weight management is selected from: 20
an obese patient with an initial body mass index $>30 \text{ kg/m}^2$;

62

an overweight patient with an initial body mass index $>27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition; and

an overweight patient with an initial body mass index $>27 \text{ kg/m}^2$ in the presence of at least one weight related comorbid condition; wherein said weight related comorbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

23. The method according to claim 19, further comprising administering a second anti-obesity agent to said individual.

24. The method according to claim 23, wherein said second anti-obesity agent is selected from: chlorphentermine, clor-
termine, phenphentermine, and phentermine, and pharmaceu-
tically acceptable salts, solvates, and hydrates thereof.

25. The method according to claim 19, further comprising administering an anti-diabetes agent to said individual.

26. The method according to claim 25, wherein said anti-diabetes agent is metformin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,365,521 B2
APPLICATION NO. : 13/820095
DATED : June 14, 2016
INVENTOR(S) : Anthony C. Blackburn et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claims:

Claim 1, Col. 59, line 37, delete "hem i" and insert -- hemi --;

Claim 1, Col. 59, line 52, delete "hem i" and insert -- hemi --;

Claim 12, Col. 60, line 33, delete "hem i" and insert -- hemi --.

Signed and Sealed this
Thirteenth Day of September, 2016

A handwritten signature in black ink, reading "Michelle K. Lee". The signature is written in a cursive, flowing style.

Michelle K. Lee
Director of the United States Patent and Trademark Office